

STABILISED INSULIN COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of International Application no. PCT/DK03/0931 filed December 22, 2003, to which priority under 35 U.S.C. 120 is claimed, the contents of which are fully incorporated herein by reference; this application also claims priority under 35 U.S.C. 119 of Danish application no. PA 2002 01991 filed December 20, 2002 and U.S. application no. 60/439,382 filed January 10, 2003, the contents of each of which are fully incorporated herein by reference.

10 FIELD OF THE INVENTION

This invention relates to insulin compositions stabilised by adding ligands for the His^{B10} Zn²⁺ sites of the R-state insulin hexamer, as well as methods for preparation and use of such preparations.

BACKGROUND OF THE INVENTION

15 Diabetes is a general term for disorders in man having excessive urine excretion as in diabetes mellitus and diabetes insipidus. Diabetes mellitus is a metabolic disorder in which the ability to utilize glucose is partly or completely lost.

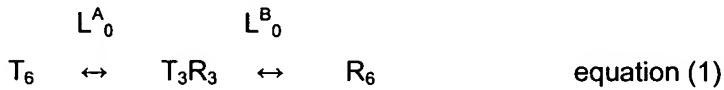
Since the discovery of insulin in the 1920's, continuous strides have been made to improve the treatment of diabetes mellitus. To help avoid extreme glycaemia levels, diabetic 20 patients often practice multiple injection therapy, whereby insulin is administered with each meal. Many diabetic patients are treated with multiple daily insulin injections in a regimen comprising one or two daily injections of a protracted insulin composition to cover the basal requirement, supplemented by bolus injections of rapid acting insulin to cover the meal-related requirements.

25 Insulin compositions having a protracted profile of action are well known in the art. Thus, one main type of such insulin compositions comprises injectable aqueous suspensions of insulin crystals or amorphous insulin. Typically, the insulin in these compositions is provided in the form of protamine insulin, zinc insulin or protamine zinc insulin

Soluble, rapid acting insulin compositions usually comprise insulin, insulin analogue or insulin 30 derivative together with zinc ion, phenolic preservative, isotonicity agent, and a buffer substance. In addition, the preparation may optionally contain some salts and/or surfactants. Such preparations contain insulin in the form of an R-state hexamer.

Insulin Allostery.

The insulin hexamer is an allosteric protein that exhibits both positive and negative cooperativity and half-of-the-sites reactivity in ligand binding. This allosteric behaviour
5 consists of two interrelated allosteric transitions designated L_0^A and L_0^B , three inter-converting allosteric conformation states (eq. 1),



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designated T_6 , T_3R_3 , and R_6 and two classes of allosteric ligand binding sites designated as the phenolic pockets and the His^{B10} anion sites. These allosteric sites are associated only with insulin subunits in the R conformation.

15 *Insulin Hexamer Structures and Ligand Binding.*

The T- to R-transition of the insulin hexamer involves transformation of the first nine residues of the B chain from an extended conformation in the T-state to an alpha-helical conformation in the R-state. This coil-to-helix transition causes the N-terminal residue,
20 Phe^{B1}, to undergo an ~ 30 Å change in position. This conformational change creates hydrophobic pockets (the phenolic pockets) at the subunit interfaces (three in T_3R_3 , and six in R_6), and the new B-chain helices form 3-helix bundles (one in T_3R_3 and two in R_6) with the bundle axis aligned along the hexamer three-fold symmetry axis. The His^{B10} Zn²⁺ in each R_3 unit is forced to change coordination geometry from octahedral to either tetrahedral
25 (monodentate ligands) or pentahedral (bidentate ligands). Formation of the helix bundle creates a narrow hydrophobic tunnel in each R_3 unit that extends from the surface ~12 Å down to the His^{B10} metal ion. This tunnel and the His^{B10} Zn²⁺ ion form the anion binding site. Ligands for the His^{B10} Zn²⁺ sites of the R-state insulin hexamer have been disclosed in US
5830999.

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Hexamer Ligand Binding and Stability of Insulin compositions.

The *in vivo* role of the T to R transition is unknown. However, the addition of allosteric ligands (e.g. phenol and chloride ion) to insulin compositions is widely used. Hexamerization is
35 driven by coordination of Zn²⁺ at the His^{B10} sites to give T_6 . Following subcutaneous injection,

some dilution of the depot will take place over time and the ligands of soluble hexamers most likely diffuse away from the protein relatively rapidly. This is probably due to one or more phenomena including the binding of Zn²⁺ by surrounding tissue and albumin, the relatively larger space available for diffusion of the hydrophobic phenolic preservatives, and the 5 generally larger diffusion coefficients characteristic of the smaller sized molecules.

Insulin compositions are usually stored for extended periods of time e.g. in vials or cartridges. Furthermore, insulin pumps are becoming more widely used, which places an additional demand on the chemical and physical stability of the insulin composition due to the 10 elevated temperatures and physical stress these preparations are exposed to. There is thus a need for insulin compositions that are more physically and chemically stable. It has been found that stabilising Zn²⁺-site ligands may be added to insulin compositions to improve these properties.

15 SUMMARY OF THE INVENTION

The present invention provides pharmaceutical compositions comprising insulin and novel ligands for the His^{B10} Zn²⁺ sites of the R-state insulin hexamer. The ligands belong to different subclasses of compounds, e.g. benzotriazoles, 3-hydroxy 2-napthoic acids, salicylic acids, 20 tetrazoles, thiazolidinediones, 5-mercaptotetrazoles, or 4-cyano-1,2,3-triazoles. The insulin may be rapid-acting. The insulin may be selected from human insulin, or an analogue or derivative thereof. The formulation may also comprise a phenolic compound, an isotonicity agent, and buffer. Also claimed are methods of treating type 1 or 2 diabetes comprising administration of a pharmaceutical composition of the invention.

25 DESCRIPTION OF THE DRAWINGS

Figures 1-8 show ThT assays of various combinations of insulin formulations and ligands of the invention.

Figure 9 shows disappearance rate of various combinations of insulin formulations and 30 ligands of the invention from the subcutaneous depot following injection in pigs.

Figures 10-14 show reverse phase chromatography of various combinations of insulin formulations and ligands of the invention.

DEFINITIONS

The following is a detailed definition of the terms used to describe the invention:

"Halogen" designates an atom selected from the group consisting of F, Cl, Br and I.

The term "alkyl" as used herein represents a saturated, branched or straight hydrocarbon group having the indicated number of carbon atoms. Representative examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, *tert*-butyl, n-pentyl, isopentyl, neopentyl, *tert*-pentyl, n-hexyl, isohexyl and the like.

The term "alkylene" as used herein represents a saturated, branched or straight bivalent hydrocarbon group having the indicated number of carbon atoms. Representative examples include, but are not limited to, methylene, 1,2-ethylene, 1,3-propylene, 1,2-propylene, 1,4-butylene, 1,5-pentylene, 1,6-hexylene, and the like.

The term "alkenyl" as used herein represents a branched or straight hydrocarbon group having the indicated number of carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl and the like.

The term "alkynyl" as used herein represents a branched or straight hydrocarbon group having the indicated number of carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentyne, 2-pentyne, 3-pentyne, 4-pentyne, 1-hexyne, 2-hexyne, 3-hexyne, 4-hexyne, 5-hexyne, 2,4-hexadiynyl and the like.

The term "alkoxy" as used herein refers to the radical -O- alkyl, wherein alkyl is as defined above. Representative examples are methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, sec-butoxy, *tert*-butoxy, pentoxy, isopentoxy, hexoxy, isohexaoxy and the like.

The term "cycloalkyl" as used herein represents a saturated, carbocyclic group having the indicated number of carbon atoms. Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

The term "cycloalkenyl" as used herein represents a non-aromatic, carbocyclic group having the indicated number of carbon atoms containing one or two double bonds. Representative examples are 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2-cyclooctenyl, 1,4-cyclooctadienyl and the like.

The term "heterocyclyl" as used herein represents a non-aromatic 3 to 10 membered ring containing one or more heteroatoms selected from nitrogen, oxygen and sulphur and optionally

containing one or two double bonds. Representative examples are pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, aziridinyl, tetrahydrofuryl and the like.

The term "aryl" as used herein is intended to include carbocyclic, aromatic ring systems such as 6 membered monocyclic and 9 to 14 membered bi- and tricyclic, carbocyclic, aromatic ring systems. Representative examples are phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, azulenyl and the like. Aryl is also intended to include the partially hydrogenated derivatives of the ring systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl and the like.

- 10 The term "arylene" as used herein is intended to include divalent, carbocyclic, aromatic ring systems such as 6 membered monocyclic and 9 to 14 membered bi- and tricyclic, divalent, carbocyclic, aromatic ring systems. Representative examples are phenylene, biphenylylene, naphthylene, anthracenylene, phenanthrenylene, fluorenylene, indenylene, azulenylene and the like. Arylene is also intended to include the partially hydrogenated derivatives of the ring systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthylene, 1,4-dihydronaphthylene and the like.
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The term "aryloxy" as used herein denotes a group -O-aryl, wherein aryl is as defined above.

The term "aroyl" as used herein denotes a group -C(O)-aryl, wherein aryl is as defined above.

- 20 The term "heteroaryl" as used herein is intended to include aromatic, heterocyclic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulphur such as 5 to 7 membered monocyclic and 8 to 14 membered bi- and tricyclic aromatic, heterocyclic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulphur. Representative examples are furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, 25 benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl, thiazolidinyl, 2-thioxothiazolidinyl and the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the ring systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuryl, 30 pyrrolinyl, pyrazolinyl, indolinyl, oxazolidinyl, oxazolinyl, oxazepinyl and the like.
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The term "heteroarylene" as used herein is intended to include divalent, aromatic, heterocyclic ring systems containing one or more heteroatoms selected from nitrogen, oxygen and sulphur such as 5 to 7 membered monocyclic and 8 to 14 membered bi- and tricyclic aromatic, heterocyclic ring systems containing one or more heteroatoms selected
5 from nitrogen, oxygen and sulphur. Representative examples are furylene, thienylene, pyrrolylene, oxazolylene, thiazolylene, imidazolylene, isoxazolylene, isothiazolylene, 1,2,3-triazolylene, 1,2,4-triazolylene, pyranylene, pyridylene, pyridazinylene, pyrimidinylene, pyrazinylene, 1,2,3-triazinylene, 1,2,4-triazinylene, 1,3,5-triazinylene, 1,2,3-oxadiazolylene,
10 1,2,4-oxadiazolylene, 1,2,5-oxadiazolylene, 1,3,4-oxadiazolylene, 1,2,3-thiadiazolylene, 1,2,4-thiadiazolylene, 1,2,5-thiadiazolylene, 1,3,4-thiadiazolylene, tetrazolylene, thiadiazinylene, indolylene, isoindolylene, benzofurylene, benzothienylene, indazolylene, benzimidazolylene, benzthiazolylene, benzisothiazolylene, benzoxazolylene, benzisoxazolylene, purinylene, quinazolinylene, quinolizinylene, quinolinylene, isoquinolinylene, quinoxalinylene, naphthyridinylene, pteridinylene, carbazolylene, azepinylene, diazepinylene, acridinylene and
15 the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the ring systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuranylene, pyrrolinylene, pyrazolinylene, indolinylene, oxazolidinylene, oxazolinylene, oxazepinylene and the like.

The term "ArG1" as used herein is intended to include an aryl or arylene radical as applicable,
20 where aryl or arylene are as defined above but limited to phenyl, biphenylyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, and azulenyl as well as the corresponding divalent radicals.

The term "ArG2" as used herein is intended to include an aryl or arylene radical as applicable, where aryl or arylene are as defined above but limited to phenyl, biphenylyl, naphthyl, fluorenyl, and indenyl, as well as the corresponding divalent radicals.
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The term "Het1" as used herein is intended to include a heteroaryl or heteroarylene radical as applicable, where heteroaryl or heteroarylene are as defined above but limited to furyl, thienyl, pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl,
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diazepinyl, acridinyl, thiazolidinyl, 2-thioxothiazolidinyl, as well as the corresponding divalent radicals.

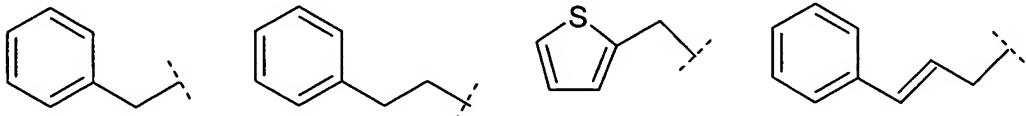
The term "Het2" as used herein is intended to include a heteroaryl or heteroarylene radical as applicable, where heteroaryl or heteroarylene are as defined above but limited to furyl, thieryl,

- 5 pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, benzimidazolyl,
- 10 benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, carbazolyl, thiazolidinyl, 2-thioxothiazolidinyl, as well as the corresponding divalent radicals.

The term "Het3" as used herein is intended to include a heteroaryl or heteroarylene radical as applicable, where heteroaryl or heteroarylene are as defined above but limited to furyl, thieryl,

- 15 pyrrolyl, pyrazolyl, 3-oxopyrazolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyridyl, tetrazolyl, indolyl, isoindolyl, benzofuryl, benzothienyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, quinolyl, isoquinolyl, quinoxalinyl, carbazolyl, thiazolidinyl, 2-thioxothiazolidinyl, as well as the corresponding divalent radicals.

- 20 "Aryl-C₁-C₆-alkyl", "heteroaryl-C₁-C₆-alkyl", "aryl-C₂-C₆-alkenyl" etc. is intended to mean C₁-C₆-alkyl or C₂-C₆-alkenyl as defined above, substituted with an aryl or heteroaryl as defined above, for example:



The term "optionally substituted" as used herein means that the groups in question are either

- 25 unsubstituted or substituted with one or more of the substituents specified. When the groups in question are substituted with more than one substituent the substituents may be the same or different.

Certain of the above defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

- 30 Furthermore, when using the terms "independently are" and "independently selected from" it should be understood that the groups in question may be the same or different.

The term "substituted with one or more substituents" as used herein is intended to include one to four substituents, such as one to three substituents, one to two substituents, or even one substituent.

5 The term "treatment" as used herein means the management and care of a patient for the purpose of combating a disease, disorder or condition. The term is intended to include the delaying of the progression of the disease, disorder or condition, the alleviation or relief of symptoms and complications, and/or the cure or elimination of the disease, disorder or condition. The patient to be treated is preferably a mammal, in particular a human being.

When in the specification or claims mention is made of groups of compounds such as
10 benzotriazoles, 3-hydroxy 2-naphthoic acids, salicylic acids, tetrazoles, thiazolidinediones, 5-mercaptotetrazoles, or 4-cyano-1,2,3-triazoles, these groups of compounds are intended to include also derivatives of the compounds from which the groups take their name.

15 The term "insulin" as used herein refers to human insulin as well as derivatives and analogues hereof as defined below.

The term "human insulin" as used herein refers to insulin naturally produced in the human body or recombinantly produced insulin identical thereto. Recombinant human insulin may be produced in any suitable host cell, for example the host cells may be bacterial, fungal (including yeast), insect, animal or plant cells.

20 The term "insulin derivative" as used herein (and related terms) refers to human insulin or an analogue thereof in which at least one organic substituent is bound to one or more of the amino acids.

By the term "analogue of human insulin" as used herein (and related terms) is meant human insulin in which one or more amino acids have been deleted and/or replaced by other amino acids, including non-codeable amino acids, or human insulin comprising additional amino acids, i.e. more than 51 amino acids, such that the resulting analogue possesses insulin activity.

30 Rapid acting insulin is intended to mean human insulin, insulin analogues or insulin derivatives having an onset of action after injection or any other form of administration faster or equal to that of soluble and neutral formulations of human insulin.

The term "phenolic compound" or similar expressions as used herein refers to a compound in which a hydroxyl group is bound directly to a benzene or substituted benzene ring. Examples of such compounds include, but are not limited to, phenol, o-cresol, m-cresol, p-cresol, chloro-cresol, thymol, and 7-hydroxyindole.

DESCRIPTION OF THE INVENTION

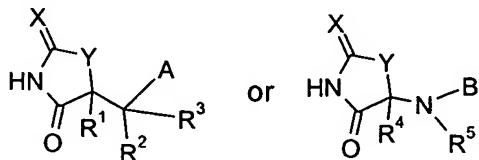
The present invention is based on the discovery that the two known ligand binding sites of the R-state insulin hexamer can be used to obtain an insulin composition having improved
5 physical and chemical stability.

The basic concept underlying the present invention involves reversible attachment of a ligand to the His^{B10} Zn²⁺ site of the R-state hexamer. The anions currently used in insulin compositions as allosteric ligands for the R-state hexamers (notably chloride ion) bind only
10 weakly to the His^{B10} anion site.

The His^{B10} Zn²⁺ site consists of a tunnel or cavity with a triangular-shaped cross-section that extends ~12 Å from the surface of the hexamer down to the His^{B10} Zn²⁺ ion. The diameter of the tunnel varies along its length and, depending on the nature of the ligand occupying the site, the opening can be capped over by the Asn^{B3} and Phe^{B1} side chains. The walls of the
15 tunnel are made up of the side chains of the amino acid residues along one face each of the three alpha-helices. The side chains from each helix that make up the lining of the tunnel are Phe^{B1}, Asn^{B3}, and Leu^{B6}. Therefore, except for the zinc ion, which is coordinated to three His^{B10} residues and is positioned at the bottom of the tunnel, the site is principally hydrophobic. Depending on the ligand structure, it may be possible for substituents on the
20 ligand to make H-bonding interactions with Asn^{B3} and with the peptide linkage to Cys^{B7}.

In one aspect the invention provides a pharmaceutical composition comprising insulin and a zinc-binding ligand which reversibly binds to a HisB10 Zn2+ site of an insulin hexamer, wherein the ligand is selected from the group consisting of benzotriazoles, 3-hydroxy 2-napthoic acids, salicylic acids, tetrazoles, thiazolidinediones, 5-mercaptotetrazoles, or 4-cyano-1,2,3-triazoles, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.
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In one embodiment the invention provides a pharmaceutical composition wherein the zinc-binding ligand is
30



wherein

X is =O, =S or =NH

Y is -S-, -O- or -NH-

R¹ and R⁴ are independently selected from hydrogen or C₁-C₆-alkyl,

5 R² is hydrogen or C₁-C₆-alkyl or aryl, R¹ and R² may optionally be combined to form a double bond,

R³ and R⁵ are independently selected from hydrogen, halogen, aryl, C₁-C₆-alkyl, or -C(O)NR¹¹R¹²,

10 A and B are independently selected from C₁-C₆-alkyl, aryl, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl or heteroaryl, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R⁶ and the aryl or heteroaryl is optionally substituted with up to four substituents R⁷, R⁸, R⁹, and R¹⁰,

A and R³ may be connected through one or two valence bonds, B and R⁵ may be connected 15 through one or two valence bonds,

R⁶ is independently selected from halogen, -CN, -CF₃, -OCF₃, aryl, -COOH and -NH₂,

R⁷, R⁸, R⁹ and R¹⁰ are independently selected from

- hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃,
20 -OCF₂CHF₂, -S(O)₂CF₃, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR¹¹, -NR¹¹R¹², -SR¹¹,
-NR¹¹S(O)₂R¹², -S(O)₂NR¹¹R¹², -S(O)NR¹¹R¹², -S(O)R¹¹, -S(O)₂R¹¹, -OS(O)₂R¹¹,
-C(O)NR¹¹R¹², -OC(O)NR¹¹R¹², -NR¹¹C(O)R¹², -CH₂C(O)NR¹¹R¹²,
-OC₁-C₆-alkyl-C(O)NR¹¹R¹², -CH₂OR¹¹, -CH₂OC(O)R¹¹, -CH₂NR¹¹R¹², -OC(O)R¹¹,
-OC₁-C₁₅-alkyl-C(O)OR¹¹, -OC₁-C₆-alkyl-OR¹¹, -SC₁-C₆-alkyl-C(O)OR¹¹,
25 -C₂-C₆-alkenyl-C(=O)OR¹¹, -NR¹¹-C(=O)-C₁-C₆-alkyl-C(=O)OR¹¹,
-NR¹¹-C(=O)-C₁-C₆-alkenyl-C(=O)OR¹¹, -C(O)OR¹¹, C(O)R¹¹, or -C₂-C₆-alkenyl-C(=O)R¹¹, =O, or -C₂-C₆-alkenyl-C(=O)-NR¹¹R¹²,

30 •C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl, each of which may optionally be substituted with one or more substituents independently selected from R¹³,

- aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, aroyl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-alkenyl, heteroaryl-C₂-C₆-alkynyl, or C₃-C₆ cycloalkyl,

of which each cyclic moiety may optionally be substituted with one or more substituents independently selected from R¹⁴,

R¹¹ and R¹² are independently selected from hydrogen, OH, C₁-C₂₀-alkyl, aryl-C₁-C₆-alkyl or 5 aryl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R¹⁵, and the aryl groups may optionally be substituted one or more substituents independently selected from R¹⁶; R¹¹ and R¹² when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, 10 oxygen and sulphur, and optionally containing one or two double bonds,

R¹³ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OR¹¹, -C(O)OR¹¹, -NR¹¹R¹², and -C(O)NR¹¹R¹²,

15 R¹⁴ is independently selected from halogen, -C(O)OR¹¹, -CH₂C(O)OR¹¹, -CH₂OR¹¹, -CN, -CF₃, -OCF₃, -NO₂, -OR¹¹, -NR¹¹R¹², S(O)₂R¹¹, aryl and C₁-C₆-alkyl,

R¹⁵ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OC₁-C₆-alkyl, -C(O)OC₁-C₆-alkyl, -COOH and -NH₂,

20 R¹⁶ is independently selected from halogen, -C(O)OC₁-C₆-alkyl, -COOH, -CN, -CF₃, -OCF₃, -NO₂, -OH, -OC₁-C₆-alkyl, -NH₂, C(=O) or C₁-C₆-alkyl, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

25 In another embodiment the invention provides a pharmaceutical composition wherein X is =O or =S.

In another embodiment the invention provides a pharmaceutical composition wherein X is =O.

30 In another embodiment the invention provides a pharmaceutical composition wherein X is =S.

In another embodiment the invention provides a pharmaceutical composition wherein Y is -O- or -S-.

35 In another embodiment the invention provides a pharmaceutical composition wherein Y is -O-.

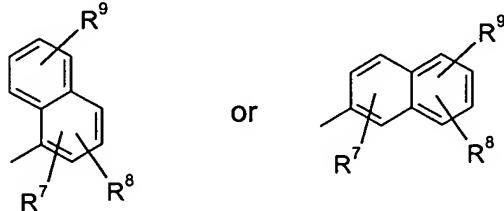
In another embodiment the invention provides a pharmaceutical composition wherein Y is -S-.

In another embodiment the invention provides a pharmaceutical composition wherein A is aryl optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the 5 same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is selected from ArG1 optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is 10 phenyl or naphtyl optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is



In another embodiment the invention provides a pharmaceutical composition wherein A is 15 phenyl.

In another embodiment the invention provides a pharmaceutical composition wherein A is heteroaryl optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is 20 selected from Het1 optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

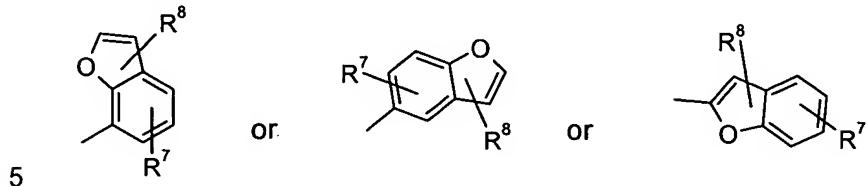
In another embodiment the invention provides a pharmaceutical composition wherein A is selected from Het2 optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

25 In another embodiment the invention provides a pharmaceutical composition wherein A is selected from Het3 optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is 30 selected from the group consisting of indolyl, benzofuranyl, quinolyl, furyl, thiienyl, or pyrrolyl, wherein each heteroaryl may optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

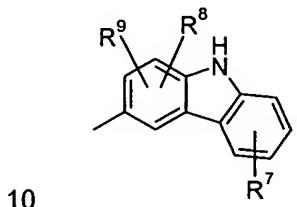
In another embodiment the invention provides a pharmaceutical composition wherein A is benzofuranyl optionally substituted with up to four substituents R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is



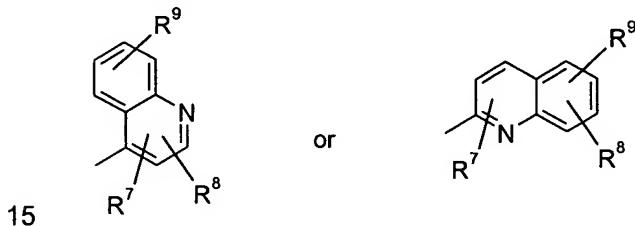
In another embodiment the invention provides a pharmaceutical composition wherein A is carbazolyl optionally substituted with up to four substituents R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is



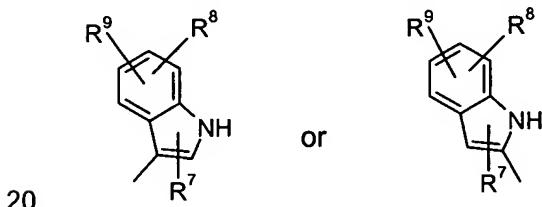
In another embodiment the invention provides a pharmaceutical composition wherein A is quinolyl optionally substituted with up to four substituents R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is



In another embodiment the invention provides a pharmaceutical composition wherein A is indolyl optionally substituted with up to four substituents R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein A is



In another embodiment the invention provides a pharmaceutical composition wherein R¹ is hydrogen.

In another embodiment the invention provides a pharmaceutical composition wherein R² is hydrogen.

5 In another embodiment the invention provides a pharmaceutical composition wherein R¹ and R² are combined to form a double bond.

In another embodiment the invention provides a pharmaceutical composition wherein R³ is C₁-C₆-alkyl, halogen, or C(O)NR¹⁶R¹⁷.

10 In another embodiment the invention provides a pharmaceutical composition wherein R³ is C₁-C₆-alkyl or C(O)NR¹⁶R¹⁷.

In another embodiment the invention provides a pharmaceutical composition wherein R³ is methyl.

15 In another embodiment the invention provides a pharmaceutical composition wherein B is phenyl optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

In another embodiment the invention provides a pharmaceutical composition wherein R⁴ is hydrogen.

In another embodiment the invention provides a pharmaceutical composition wherein R⁵ is hydrogen.

20 In another embodiment the invention provides a pharmaceutical composition wherein R⁶ is aryl.

In another embodiment the invention provides a pharmaceutical composition wherein R⁶ is phenyl.

25 In another embodiment the invention provides a pharmaceutical composition wherein R⁷, R⁸, R⁹ and R¹⁰ are independently selected from

•hydrogen, halogen, -NO₂, -OR¹¹, -NR¹¹R¹², -SR¹¹, -NR¹¹S(O)₂R¹², -S(O)₂NR¹¹R¹², -S(O)NR¹¹R¹², -S(O)R¹¹, -S(O)₂R¹¹, -OS(O)₂ R¹¹, -NR¹¹C(O)R¹², -CH₂OR¹¹, -CH₂OC(O)R¹¹, -CH₂NR¹¹R¹², -OC(O)R¹¹, -OC₁-C₆-alkyl-C(O)OR¹¹, -OC₁-C₆-alkyl-C(O)NR¹¹R¹², -OC₁-C₆-alkyl-OR¹¹, -SC₁-C₆-alkyl-C(O)OR¹¹, -C₂-C₆-alkenyl-C(=O)OR¹¹, -C(O)OR¹¹, or -C₂-C₆-alkenyl-C(=O)R¹¹,

•C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl, which may each optionally be substituted with one or more substituents independently selected from R¹³

•aryl, aryloxy, aroyl, arylsulfanyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, aroyl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, wherein each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R¹⁴

5

In another embodiment the invention provides a pharmaceutical composition wherein R⁷, R⁸, R⁹ and R¹⁰ are independently selected from

10 •hydrogen, halogen, -NO₂, -OR¹¹, -NR¹¹R¹², -SR¹¹, -S(O)₂R¹¹, -OS(O)₂R¹¹, -CH₂OC(O)R¹¹, -OC(O)R¹¹, -OC₁-C₆-alkyl-C(O)OR¹¹, -OC₁-C₆-alkyl-OR¹¹, -SC₁-C₆-alkyl-C(O)OR¹¹, -C(O)OR¹¹, or -C₂-C₆-alkenyl-C(=O)R¹¹,

•C₁-C₆-alkyl or C₁-C₆-alkenyl which may each optionally be substituted with one or more substituents independently selected from R¹³

15

•aryl, aryloxy, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, heteroaryl,

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R¹⁴

20

In another embodiment the invention provides a pharmaceutical composition wherein R⁷, R⁸, R⁹ and R¹⁰ are independently selected from

25 •hydrogen, halogen, -NO₂, -OR¹¹, -NR¹¹R¹², -SR¹¹, -S(O)₂R¹¹, -OS(O)₂R¹¹, -CH₂OC(O)R¹¹, -OC(O)R¹¹, -OC₁-C₆-alkyl-C(O)OR¹¹, -OC₁-C₆-alkyl-OR¹¹, -SC₁-C₆-alkyl-C(O)OR¹¹, -C(O)OR¹¹, or -C₂-C₆-alkenyl-C(=O)R¹¹,

•C₁-C₆-alkyl or C₁-C₆- which may each optionally be substituted with one or more substituents independently selected from R¹³

30

•aryl, aryloxy, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, heteroaryl,

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R¹⁴.

35

In another embodiment the invention provides a pharmaceutical composition wherein R⁷, R⁸, R⁹ and R¹⁰ are independently selected from

- hydrogen, halogen, -OR¹¹, -OC₁-C₆-alkyl-C(O)OR¹¹, or -C(O)OR¹¹,

5 • C₁-C₆-alkyl which may each optionally be substituted with one or more substituents independently selected from R¹³

- aryl, aryloxy, aryl-C₁-C₆-alkoxy,

10 of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R¹⁴.

In another embodiment the invention provides a pharmaceutical composition wherein R⁷, R⁸, R⁹ and R¹⁰ are independently selected from

15 • hydrogen, halogen, -OR¹¹, -OC₁-C₆-alkyl-C(O)OR¹¹, or -C(O)OR¹¹,

- C₁-C₆-alkyl which may optionally be substituted with one or more substituents independently selected from R¹³

20 • phenyl, phenoxy, phenyl-C₁-C₆-alkoxy, wherein each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R¹⁴.

In another embodiment the invention provides a pharmaceutical composition wherein R¹¹ and R¹² are independently selected from hydrogen, C₁-C₂₀-alkyl, aryl or aryl-C₁-C₆-alkyl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R¹⁵, and the aryl groups may optionally be substituted one or more substituents independently selected from R¹⁶; R¹¹ and R¹² when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds.

In another embodiment the invention provides a pharmaceutical composition wherein R¹¹ and R¹² are independently selected from hydrogen, C₁-C₂₀-alkyl, aryl or aryl-C₁-C₆-alkyl, wherein the alkyl groups may optionally be substituted with one or more substituents independently

selected from R^{15} , and the aryl groups may optionally be substituted one or more substituents independently selected from R^{16} .

In another embodiment the invention provides a pharmaceutical composition wherein R^{11} and R^{12} are independently selected from phenyl or phenyl-C₁-C₆-alkyl.

5 In another embodiment the invention provides a pharmaceutical composition wherein one or both of R^{11} and R^{12} are methyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{13} is independently selected from halogen, CF₃, OR¹¹ or NR¹¹R¹².

10 In another embodiment the invention provides a pharmaceutical composition wherein R^{13} is independently selected from halogen or OR¹¹.

In another embodiment the invention provides a pharmaceutical composition wherein R^{13} is OR¹¹.

In another embodiment the invention provides a pharmaceutical composition wherein R^{14} is independently selected from halogen, -C(O)OR¹¹, -CN, -CF₃, -OR¹¹, S(O)₂R¹¹, and C₁-C₆-alkyl.

15 In another embodiment the invention provides a pharmaceutical composition wherein R^{14} is independently selected from halogen, -C(O)OR¹¹, or -OR¹¹.

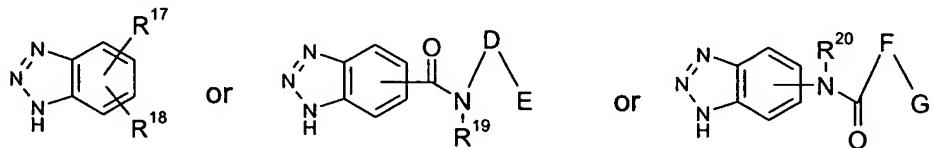
In another embodiment the invention provides a pharmaceutical composition wherein R^{15} is independently selected from halogen, -CN, -CF₃, -C(O)OC₁-C₆-alkyl, and -COOH.

20 In another embodiment the invention provides a pharmaceutical composition wherein R^{15} is independently selected from halogen or -C(O)OC₁-C₆-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein R^{16} is independently selected from halogen, -C(O)OC₁-C₆-alkyl, -COOH, -NO₂, -OC₁-C₆-alkyl, -NH₂, C(=O) or C₁-C₆-alkyl.

25 In another embodiment the invention provides a pharmaceutical composition wherein R^{16} is independently selected from halogen, -C(O)OC₁-C₆-alkyl, -COOH, -NO₂, or C₁-C₆-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein the zinc-binding ligand is



30

wherein

R^{19} is hydrogen or C₁-C₆-alkyl,

R²⁰ is hydrogen or C₁-C₆-alkyl,

D and F are a valence bond or C₁-C₆-alkylene optionally substituted with one or more substituents independently selected from R⁷²,

5

R⁷² is independently selected from hydroxy, C₁-C₆-alkyl, or aryl,

E is C₁-C₆-alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents R²¹, R²² and R²³,

10 G is C₁-C₆-alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents R²⁴, R²⁵ and R²⁶,

R¹⁷, R¹⁸, R²¹, R²², R²³, R²⁴, R²⁵ and R²⁶ are independently selected from

15 •hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -S(O)₂CF₃, -SCF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷S(O)₂R²⁸, -S(O)₂NR²⁷R²⁸, -S(O)NR²⁷R²⁸, -S(O)R²⁷, -S(O)₂R²⁷, -C(O)NR²⁷R²⁸, -OC(O)NR²⁷R²⁸, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -CH₂C(O)NR²⁷R²⁸, -OCH₂C(O)NR²⁷R²⁸, -CH₂OR²⁷, -CH₂NR²⁷R²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-

20 alkenyl-C(=O)OR²⁷, -NR²⁷-C(=O)-C₁-C₆-alkyl-C(=O)OR²⁷, -NR²⁷-C(=O)-C₁-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or -C(O)OR²⁷,

•C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl,

25

which may optionally be substituted with one or more substituents independently selected from R²⁹,

30 •aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-alkenyl or heteroaryl-C₂-C₆-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰,

35

R²⁷ and R²⁸ are independently selected from hydrogen, C₁-C₆-alkyl, aryl-C₁-C₆-alkyl or aryl, or R²⁷ and R²⁸ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further 5 heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R²⁹ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OR²⁷, and -NR²⁷R²⁸,

10 R³⁰ is independently selected from halogen, -C(O)OR²⁷, -CN, -CF₃, -OCF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸ and C₁-C₆-alkyl, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

In another embodiment the invention provides a pharmaceutical composition wherein D is a valence bond.

15 In another embodiment the invention provides a pharmaceutical composition wherein D is C₁-C₆-alkylene optionally substituted with one or more hydroxy, C₁-C₆-alkyl, or aryl.

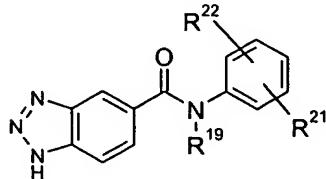
In another embodiment the invention provides a pharmaceutical composition wherein E is aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents independently selected from R²¹, R²² and R²³.

20 In another embodiment the invention provides a pharmaceutical composition wherein E is aryl optionally substituted with up to three substituents independently selected from R²¹, R²² and R²³.

In another embodiment the invention provides a pharmaceutical composition wherein E is selected from ArG1 and optionally substituted with up to three substituents independently 25 selected from R²¹, R²² and R²³.

In another embodiment the invention provides a pharmaceutical composition wherein E is phenyl optionally substituted with up to three substituents independently selected from R²¹, R²² and R²³.

30 In another embodiment the invention provides a pharmaceutical composition wherein the zinc-binding ligand is



In another embodiment the invention provides a pharmaceutical composition wherein R²¹, R²² and R²³ are independently selected from

- 5 • hydrogen, halogen, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -C(O)NR²⁷R²⁸, -OC(O)NR²⁷R²⁸, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -CH₂C(O)NR²⁷R²⁸, -OCH₂C(O)NR²⁷R²⁸, -CH₂OR²⁷, -CH₂NR²⁷R²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷, -NR²⁷-C(=O)-C₁-C₆-alkyl-C(=O)OR²⁷, -NR²⁷-C(=O)-C₁-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or
10 -C(O)OR²⁷,
- C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl,

15 which may optionally be substituted with one or more substituents independently selected from R²⁹

20 • aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-alkenyl or heteroaryl-C₂-C₆-alkynyl,

25 of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment the invention provides a pharmaceutical composition wherein R²¹, R²² and R²³ are independently selected from

- 30 • hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or -C(O)OR²⁷,
- C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R²⁹

- aryl, aryloxy, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, heteroaryl, heteroaryl-C₁-C₆-alkyl,

of which the cyclic moieties optionally may be substituted with one or more
5 substituents selected from R³⁰.

In another embodiment the invention provides a pharmaceutical composition wherein R²¹, R²² and R²³ are independently selected from

- 10 • hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or -C(O)OR²⁷,

- 15 • methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R²⁹

- aryl, aryloxy, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, heteroaryl, heteroaryl-C₁-C₆-alkyl

20 of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment the invention provides a pharmaceutical composition wherein R²¹, R²² and R²³ are independently selected from

- 25 • hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or -C(O)OR²⁷,

- 30 • methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R²⁹

- ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C₁-C₆-alkoxy, ArG1-C₁-C₆-alkyl, Het3, Het3-C₁-C₆-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment the invention provides a pharmaceutical composition wherein R²¹, R²² and R²³ are independently selected from

5

- hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or -C(O)OR²⁷,

10

- C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R²⁹

- phenyl, phenoxy, phenyl-C₁-C₆-alkoxy, phenyl-C₁-C₆-alkyl,

15 of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment the invention provides a pharmaceutical composition wherein R¹⁹ is hydrogen or methyl.

20 In another embodiment the invention provides a pharmaceutical composition wherein R¹⁹ is hydrogen.

In another embodiment the invention provides a pharmaceutical composition wherein R²⁷ is Hydrogen, C₁-C₆-alkyl or aryl.

25 In another embodiment the invention provides a pharmaceutical composition wherein R²⁷ is hydrogen or C₁-C₆-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein R²⁸ is hydrogen or C₁-C₆-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein F is a valence bond.

30 In another embodiment the invention provides a pharmaceutical composition wherein F is C₁-C₆-alkylene optionally substituted with one or more hydroxy, C₁-C₆-alkyl, or aryl.

In another embodiment the invention provides a pharmaceutical composition wherein G is C₁-C₆-alkyl or aryl, wherein the aryl is optionally substituted with up to three substituents R²⁴, R²⁵ and R²⁶.

In another embodiment the invention provides a pharmaceutical composition wherein G is C₁-C₆-alkyl or ArG1, wherein the aryl is optionally substituted with up to three substituents R²⁴, R²⁵ and R²⁶.

5 In another embodiment the invention provides a pharmaceutical composition wherein G is C₁-C₆-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein G is phenyl optionally substituted with up to three substituents R²⁴, R²⁵ and R²⁶.

In another embodiment the invention provides a pharmaceutical composition wherein R²⁴, R²⁵ and R²⁶ are independently selected from

10

- hydrogen, halogen, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -C(O)NR²⁷R²⁸, -OC(O)NR²⁷R²⁸, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -CH₂C(O)NR²⁷R²⁸, -OCH₂C(O)NR²⁷R²⁸, -CH₂OR²⁷, -CH₂NR²⁷R²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-15 C(=O)OR²⁷, -NR²⁷-C(=O)-C₁-C₆-alkyl-C(=O)OR²⁷, -NR²⁷-C(=O)-C₁-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or -C(O)OR²⁷,
- C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl,

20

which may optionally be substituted with one or more substituents independently selected from R²⁹

25

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-alkenyl or heteroaryl-C₂-C₆-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

30

In another embodiment the invention provides a pharmaceutical composition wherein R²⁴, R²⁵ and R²⁶ are independently selected from

35

- hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-

C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or
-C(O)OR²⁷,

- C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl,

5

which may optionally be substituted with one or more substituents independently selected from R²⁹

- 10
- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-alkenyl or heteroaryl-C₂-C₆-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

15

In another embodiment the invention provides a pharmaceutical composition wherein R²⁴, R²⁵ and R²⁶ are independently selected from

- 20
- hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸,
-OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷,
-C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or
-C(O)OR²⁷,

- 25
- C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R²⁹

• aryl, aryloxy, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, heteroaryl, heteroaryl-C₁-C₆-alkyl,

30

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment the invention provides a pharmaceutical composition wherein R²¹, R²² and R²³ are independently selected from

35

- hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or -C(O)OR²⁷,

5

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R²⁹

10

- ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C₁-C₆-alkoxy, ArG1-C₁-C₆-alkyl, Het3, Het3-C₁-C₆-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment the invention provides a pharmaceutical composition wherein R²¹, R²² and R²³ are independently selected from

15

- hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or -C(O)OR²⁷,

20

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R²⁹

25

- ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C₁-C₆-alkoxy, ArG1-C₁-C₆-alkyl, Het3, Het3-C₁-C₆-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment the invention provides a pharmaceutical composition wherein R²¹, R²² and R²³ are independently selected from

30

- hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or -C(O)OR²⁷,

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R²⁹
- 5 • ArG1, ArG1-O-, ArG1-C₁-C₆-alkoxy, ArG1-C₁-C₆-alkyl,
of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.
- In another embodiment the invention provides a pharmaceutical composition wherein R²⁰ is hydrogen or methyl.
- 10 In another embodiment the invention provides a pharmaceutical composition wherein R²⁰ is hydrogen.
- In another embodiment the invention provides a pharmaceutical composition wherein R²⁷ is hydrogen, C₁-C₆-alkyl or aryl.
- In another embodiment the invention provides a pharmaceutical composition wherein R²⁷ is hydrogen or C₁-C₆-alkyl or ArG1.
- 15 In another embodiment the invention provides a pharmaceutical composition wherein R²⁷ is hydrogen or C₁-C₆-alkyl.
- In another embodiment the invention provides a pharmaceutical composition wherein R²⁸ is hydrogen or C₁-C₆-alkyl.
- 20 In another embodiment the invention provides a pharmaceutical composition wherein R¹⁷ and R¹⁸ are independently selected from
- hydrogen, halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -S(O)R²⁷, -S(O)₂R²⁷, -C(O)NR²⁷R²⁸, -CH₂OR²⁷, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, or -C(O)OR²⁷,
- 25 • C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl, optionally substituted with one or more substituents independently selected from R²⁹
- 30 • aryl, aryloxy, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, heteroaryl, heteroaryl-C₁-C₆-alkyl,
of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment the invention provides a pharmaceutical composition wherein R¹⁷ and R¹⁸ are independently selected from

- hydrogen, halogen, -CN, -CF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸, or -C(O)OR²⁷,
- 5 • C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R²⁹
- 10 • aryl, aryloxy, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, heteroaryl, heteroaryl-C₁-C₆-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

15 In another embodiment the invention provides a pharmaceutical composition wherein R¹⁷ and R¹⁸ are independently selected from

- hydrogen, halogen, -CN, -CF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸, or -C(O)OR²⁷
- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R²⁹
- 20 • aryl, aryloxy, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, heteroaryl, heteroaryl-C₁-C₆-alkyl
of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment the invention provides a pharmaceutical composition wherein R¹⁷ and R¹⁸ are independently selected from

- hydrogen, halogen, -CN, -CF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸, or -C(O)OR²⁷
- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R²⁹
- 30 • ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C₁-C₆-alkoxy, ArG1-C₁-C₆-alkyl, Het3, Het3-C₁-C₆-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment the invention provides a pharmaceutical composition wherein R¹⁷ and R¹⁸ are independently selected from

- 35 • hydrogen, halogen, -CN, -CF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸, or -C(O)OR²⁷

• C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R²⁹

• phenyl, phenoxy, phenyl-C₁-C₆-alkoxy, phenyl-C₁-C₆-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment the invention provides a pharmaceutical composition wherein R²⁷ is hydrogen or C₁-C₆-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein R²⁷ is hydrogen, methyl or ethyl.

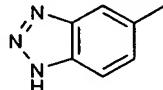
10 In another embodiment the invention provides a pharmaceutical composition wherein R²⁸ is hydrogen or C₁-C₆-alkyl.

In another embodiment the invention provides a pharmaceutical composition wherein R²⁸ is hydrogen, methyl or ethyl.

In another embodiment the invention provides a pharmaceutical composition wherein R⁷² is

15 -OH or phenyl.

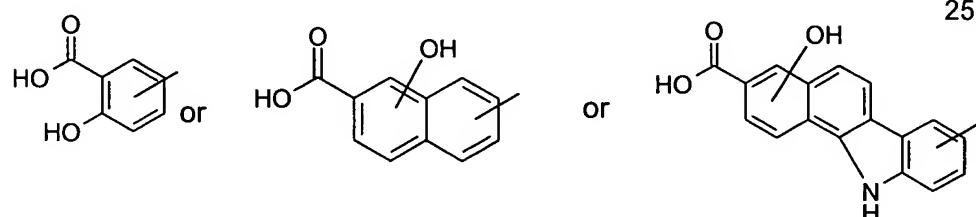
In another embodiment the invention provides a pharmaceutical composition wherein the zinc-binding ligand is



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In another embodiment the invention provides a pharmaceutical composition wherein the zinc-binding ligand is of the form H-I-J

wherein H is

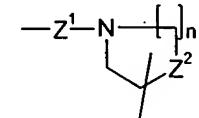


30

wherein the phenyl, naphthalene or benzocarbazole rings are optionally substituted with one or more substituents independently selected from R³¹

I is selected from

- a valence bond,
- $-\text{CH}_2\text{N}(\text{R}^{32})-$ or $-\text{SO}_2\text{N}(\text{R}^{33})-$,



- wherein Z^1 is $\text{S}(\text{O})_2$ or CH_2 , Z^2 is $-\text{NH}-$, $-\text{O}-$ or $-\text{S}-$, and n is 1 or 2,

5

J is

- $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_2\text{-C}_6\text{-alkenyl}$ or $\text{C}_2\text{-C}_6\text{-alkynyl}$, which may each optionally be substituted with one or more substituents selected from R^{34} ,
- Aryl, aryloxy, aryl-oxygenocarbonyl-, aroyl, aryl- $\text{C}_1\text{-C}_6\text{-alkoxy}$ -, aryl- $\text{C}_1\text{-C}_6\text{-alkyl}$ -, aryl- $\text{C}_2\text{-C}_6\text{-alkenyl}$ -, aryl- $\text{C}_2\text{-C}_6\text{-alkynyl}$ -, heteroaryl, heteroaryl- $\text{C}_1\text{-C}_6\text{-alkyl}$ -, heteroaryl- $\text{C}_2\text{-C}_6\text{-alkenyl}$ - or heteroaryl- $\text{C}_2\text{-C}_6\text{-alkynyl}$ -, wherein the cyclic moieties are optionally substituted with one or more substituents selected from R^{37} ,
- hydrogen,

- 15 R^{31} is independently selected from hydrogen, halogen, $-\text{CN}$, $-\text{CH}_2\text{CN}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{S}(\text{O})_2\text{CF}_3$, $-\text{SCF}_3$, $-\text{NO}_2$, $-\text{OR}^{35}$, $-\text{C}(\text{O})\text{R}^{35}$, $-\text{NR}^{35}\text{R}^{36}$, $-\text{SR}^{35}$, $-\text{NR}^{35}\text{S}(\text{O})_2\text{R}^{36}$, $-\text{S}(\text{O})_2\text{NR}^{35}\text{R}^{36}$, $-\text{S}(\text{O})\text{NR}^{35}\text{R}^{36}$, $-\text{S}(\text{O})\text{R}^{35}$, $-\text{S}(\text{O})_2\text{R}^{35}$, $-\text{C}(\text{O})\text{NR}^{35}\text{R}^{36}$, $-\text{OC}(\text{O})\text{NR}^{35}\text{R}^{36}$, $-\text{NR}^{35}\text{C}(\text{O})\text{R}^{36}$, $-\text{CH}_2\text{C}(\text{O})\text{NR}^{35}\text{R}^{36}$, $-\text{OCH}_2\text{C}(\text{O})\text{NR}^{35}\text{R}^{36}$, $-\text{CH}_2\text{OR}^{35}$, $-\text{CH}_2\text{NR}^{35}\text{R}^{36}$, $-\text{OC}(\text{O})\text{R}^{35}$, $-\text{OC}_1\text{-C}_6\text{-alkyl-C}(\text{O})\text{OR}^{35}$, $-\text{SC}_1\text{-C}_6\text{-alkyl-C}(\text{O})\text{OR}^{35}$ $-\text{C}_2\text{-C}_6\text{-alkenyl-C}(\text{=O})\text{OR}^{35}$, $-\text{C}_1\text{-C}_6\text{-alkyl-C}(\text{=O})\text{OR}^{35}$, $-\text{C}_1\text{-C}_6\text{-alkenyl-C}(\text{=O})\text{OR}^{35}$, $-\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-alkanoyl}$ or $-\text{C}(\text{O})\text{OR}^{35}$,

R^{32} and R^{33} are independently selected from hydrogen, $\text{C}_1\text{-C}_6\text{-alkyl}$ or $\text{C}_1\text{-C}_6\text{-alkanoyl}$,

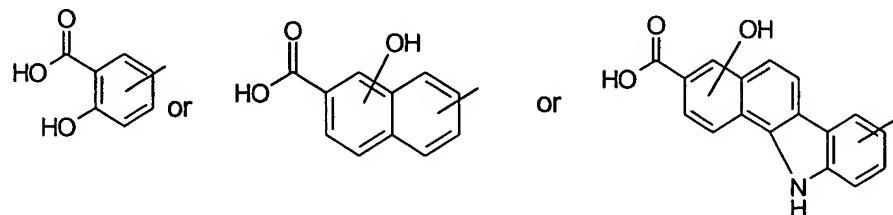
- 25 R^{34} is independently selected from halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^{35}$, and $-\text{NR}^{35}\text{R}^{36}$,

- 30 R^{35} and R^{36} are independently selected from hydrogen, $\text{C}_1\text{-C}_6\text{-alkyl}$, aryl- $\text{C}_1\text{-C}_6\text{-alkyl}$ or aryl, or R^{35} and R^{36} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{37} is independently selected from halogen, $-C(O)OR^{35}$, $-C(O)H$, $-CN$, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$, $C_1\text{-}C_6\text{-alkyl}$ or $C_1\text{-}C_6\text{-alkanoyl}$,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt
5 thereof with a pharmaceutically acceptable acid or base.

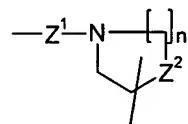
In another embodiment the invention provides a pharmaceutical composition wherein the zinc-binding ligand is of the form H-I-J, wherein H is



wherein the phenyl, naphthalene or benzocarbazole rings are optionally substituted with one
10 or more substituents independently selected from R^{31} ,

I is selected from

- a valence bond,
- $-CH_2N(R^{32})-$ or $-SO_2N(R^{33})-$,



15 • wherein Z^1 is $S(O)_2$ or CH_2 , Z^2 is $N\text{-}O$ -or $-S\text{-}$, and n is 1 or 2,

J is

- $C_1\text{-}C_6\text{-alkyl}$, $C_2\text{-}C_6\text{-alkenyl}$ or $C_2\text{-}C_6\text{-alkynyl}$, which may each optionally be substituted with one or more substituents selected from R^{34} ,
- 20 • Aryl, aryloxy, aryl-oxycarbonyl-, aroyl, aryl- $C_1\text{-}C_6\text{-alkoxy}$ -, aryl- $C_1\text{-}C_6\text{-alkyl}$ -, aryl- $C_2\text{-}C_6\text{-alkenyl}$ -, aryl- $C_2\text{-}C_6\text{-alkynyl}$ -, heteroaryl, heteroaryl- $C_1\text{-}C_6\text{-alkyl}$ -, heteroaryl- $C_2\text{-}C_6\text{-alkenyl}$ - or heteroaryl- $C_2\text{-}C_6\text{-alkynyl}$ -, wherein the cyclic moieties are optionally substituted with one or more substituents selected from R^{37} ,
- 25 • hydrogen,

R^{31} is independently selected from hydrogen, halogen, $-CN$, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{35}$, $-C(O)R^{35}$, $-NR^{35}R^{36}$, $-SR^{35}$,

- NR³⁵S(O)₂R³⁶, -S(O)₂NR³⁵R³⁶, -S(O)NR³⁵R³⁶, -S(O)R³⁵, -S(O)₂R³⁵, -C(O)NR³⁵R³⁶,
 -OC(O)NR³⁵R³⁶, -NR³⁵C(O)R³⁶, -CH₂C(O)NR³⁵R³⁶, -OCH₂C(O)NR³⁵R³⁶, -CH₂OR³⁵,
 -CH₂NR³⁵R³⁶, -OC(O)R³⁵, -OC₁-C₆-alkyl-C(O)OR³⁵, -SC₁-C₆-alkyl-C(O)OR³⁵ -C₂-C₆-alkenyl-
 C(=O)OR³⁵, -NR³⁵-C(=O)-C₁-C₆-alkyl-C(=O)OR³⁵, -NR³⁵-C(=O)-C₁-C₆-alkenyl-C(=O)OR³⁵-,
 5 C₁-C₆-alkyl, C₁-C₆-alkanoyl or -C(O)OR³⁵,

R³² and R³³ are independently selected from hydrogen, C₁-C₆-alkyl or C₁-C₆-alkanoyl,

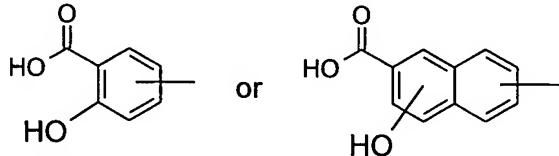
R³⁴ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OR³⁵, and -NR³⁵R³⁶,

- 10 R³⁵ and R³⁶ are independently selected from hydrogen, C₁-C₆-alkyl, aryl-C₁-C₆-alkyl or aryl, or
 R³⁵ and R³⁶ when attached to the same nitrogen atom together with the said nitrogen atom
 may form a 3 to 8 membered heterocyclic ring optionally containing one or two further
 heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or
 15 two double bonds,

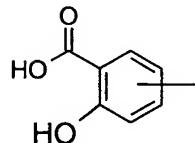
R³⁷ is independently selected from halogen, -C(O)OR³⁵, -C(O)H, -CN, -CF₃, -OCF₃, -NO₂, -
 OR³⁵, -NR³⁵R³⁶, C₁-C₆-alkyl or C₁-C₆-alkanoyl,

- 20 or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt
 thereof with a pharmaceutically acceptable acid or base,
 With the proviso that R³¹ and J cannot both be hydrogen.

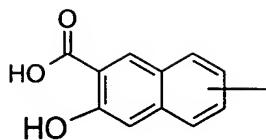
In another embodiment the invention provides a pharmaceutical composition wherein H is



- 25 In another embodiment the invention provides a pharmaceutical composition wherein H is



In another embodiment the invention provides a pharmaceutical composition wherein H is



In another embodiment the invention provides a pharmaceutical composition wherein I is a valence bond, $-\text{CH}_2\text{N}(\text{R}^{32})-$, or $-\text{SO}_2\text{N}(\text{R}^{33})-$.

5 In another embodiment the invention provides a pharmaceutical composition wherein I is a valence bond.

In another embodiment the invention provides a pharmaceutical composition wherein J is

- hydrogen,
- $\text{C}_1\text{-C}_6$ -alkyl, $\text{C}_2\text{-C}_6$ -alkenyl or $\text{C}_2\text{-C}_6$ -alkynyl,

which may optionally be substituted with one or more substituents selected from 10 halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^{35}$, and $-\text{NR}^{35}\text{R}^{36}$,

- aryl, or heteroaryl, wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37} .

In another embodiment the invention provides a pharmaceutical composition wherein J is

- hydrogen,
- aryl or heteroaryl, wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37} .

In another embodiment the invention provides a pharmaceutical composition wherein J is

- hydrogen,
- ArG1 or Het3 , wherein the cyclic moieties are optionally substituted with one or 20 more substituents independently selected from R^{37} .

In another embodiment the invention provides a pharmaceutical composition wherein J is

- hydrogen,
- phenyl or naphthyl optionally substituted with one or more substituents independently selected from R^{37} .

25 In another embodiment the invention provides a pharmaceutical composition wherein J is hydrogen.

In another embodiment the invention provides a pharmaceutical composition wherein R^{32} and R^{33} are independently selected from hydrogen or $\text{C}_1\text{-C}_6$ -alkyl.

30 In another embodiment the invention provides a pharmaceutical composition wherein R^{34} is hydrogen, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{SCF}_3$, $-\text{NO}_2$, $-\text{OR}^{35}$, $-\text{C}(\text{O})\text{R}^{35}$, $-\text{NR}^{35}\text{R}^{36}$, $-\text{SR}^{35}$,

$-C(O)NR^{35}R^{36}$, $-OC(O)NR^{35}R^{36}$, $-NR^{35}C(O)R^{36}$, $-OC(O)R^{35}$, $-OC_1-C_6\text{-alkyl}-C(O)OR^{35}$, $-SC_1-C_6\text{-alkyl}-C(O)OR^{35}$ or $-C(O)OR^{35}$.

In another embodiment the invention provides a pharmaceutical composition wherein R^{34} is hydrogen, halogen, $-CF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$, $-SR^{35}$, $-NR^{35}C(O)R^{36}$, or $-C(O)OR^{35}$.

5 In another embodiment the invention provides a pharmaceutical composition wherein R^{34} is hydrogen, halogen, $-CF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$, or $-NR^{35}C(O)R^{36}$.

In another embodiment the invention provides a pharmaceutical composition wherein R^{34} is hydrogen, halogen, or $-OR^{35}$.

10 In another embodiment the invention provides a pharmaceutical composition wherein R^{35} and R^{36} are independently selected from hydrogen, $C_1-C_6\text{-alkyl}$, or aryl.

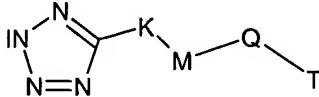
In another embodiment the invention provides a pharmaceutical composition wherein R^{35} and R^{36} are independently selected from hydrogen or $C_1-C_6\text{-alkyl}$.

In another embodiment the invention provides a pharmaceutical composition wherein R^{37} is halogen, $-C(O)OR^{35}$, $-CN$, $-CF_3$, $-OR^{35}$, $-NR^{35}R^{36}$, $C_1-C_6\text{-alkyl}$ or $C_1-C_6\text{-alkanoyl}$.

15 In another embodiment the invention provides a pharmaceutical composition wherein R^{37} is halogen, $-C(O)OR^{35}$, $-OR^{35}$, $-NR^{35}R^{36}$, $C_1-C_6\text{-alkyl}$ or $C_1-C_6\text{-alkanoyl}$.

In another embodiment the invention provides a pharmaceutical composition wherein R^{37} is halogen, $-C(O)OR^{35}$ or $-OR^{35}$.

20 In another embodiment the invention provides a pharmaceutical composition wherein the zinc-binding ligand is



wherein K is a valence bond, $C_1-C_6\text{-alkylene}$, $-NH-C(=O)-U-$, $-C_1-C_6\text{-alkyl-S-}$, $-C_1-C_6\text{-alkyl-O-}$, $-C(=O)-$, or $-C(=O)-NH-$, wherein any $C_1-C_6\text{-alkyl}$ moiety is optionally substituted with R^{38} ,

25

U is a valence bond, $C_1-C_6\text{-alkenylene}$, $-C_1-C_6\text{-alkyl-O-}$ or $C_1-C_6\text{-alkylene}$ wherein any $C_1-C_6\text{-alkyl}$ moiety is optionally substituted with $C_1-C_6\text{-alkyl}$,

30 R^{38} is $C_1-C_6\text{-alkyl}$, aryl, wherein the alkyl or aryl moieties are optionally substituted with one or more substituents independently selected from R^{39} ,

R^{39} is independently selected from halogen, cyano, nitro, amino,

M is a valence bond, arylene or heteroarylene, wherein the aryl or heteroaryl moieties are optionally substituted with one or more substituents independently selected from R⁴⁰,

R⁴⁰ is selected from

- 5 •hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃,
-OCF₂CHF₂, -S(O)₂CF₃, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR⁴¹, -NR⁴¹R⁴², -SR⁴¹,
-NR⁴¹S(O)R⁴², -S(O)₂NR⁴¹R⁴², -S(O)NR⁴¹R⁴², -S(O)R⁴¹, -S(O)₂R⁴¹, -OS(O)₂R⁴¹,
-C(O)NR⁴¹R⁴², -OC(O)NR⁴¹R⁴², -NR⁴¹C(O)R⁴², -CH₂C(O)NR⁴¹R⁴², -OC₁-C₆-alkyl-C(O)NR⁴¹R⁴², -CH₂OR⁴¹, -CH₂OC(O)R⁴¹, -CH₂NR⁴¹R⁴², -OC(O)R⁴¹, -OC₁-C₆-alkyl-C(O)OR⁴¹, -OC₁-C₆-alkyl-OR⁴¹, -S-C₁-C₆-alkyl-C(O)OR⁴¹, -C₂-C₆-alkenyl-C(=O)OR⁴¹, -NR⁴¹-C(=O)-C₁-C₆-alkyl-C(=O)OR⁴¹, -NR⁴¹-C(=O)-C₁-C₆-alkenyl-C(=O)OR⁴¹, -C(O)OR⁴¹, -C₂-C₆-alkenyl-C(=O)R⁴¹, =O, -NH-C(=O)-O-C₁-C₆-alkyl, or -NH-C(=O)-C(=O)-O-C₁-C₆-alkyl,
- 10 •C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl, which may each optionally be substituted with one or more substituents selected from R⁴³,
- 15 •aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, aroyl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-alkenyl or heteroaryl-C₂-C₆-alkynyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R⁴⁴,

- 20 R⁴¹ and R⁴² are independently selected from hydrogen, -OH, C₁-C₆-alkyl, C₁-C₆-alkenyl, aryl-C₁-C₆-alkyl or aryl, wherein the alkyl moieties may optionally be substituted with one or more substituents independently selected from R⁴⁵, and the aryl moieties may optionally be substituted with one or more substituents independently selected from R⁴⁶; R⁴¹ and R⁴² when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms
- 25 selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,
- 30 R⁴³ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OR⁴¹, and -NR⁴¹R⁴²

R⁴⁴ is independently selected from halogen, -C(O)OR⁴¹, -CH₂C(O)OR⁴¹, -CH₂OR⁴¹, -CN, -CF₃, -OCF₃, -NO₂, -OR⁴¹, -NR⁴¹R⁴² and C₁-C₆-alkyl,

R⁴⁵ is independently selected from halogen, -CN, -CF₃, -OCF₃, -O-C₁-C₆-alkyl, -C(O)-O-C₁-C₆-alkyl, -COOH and -NH₂,

5 R⁴⁶ is independently selected from halogen, -C(O)OC₁-C₆-alkyl, -COOH, -CN, -CF₃, -OCF₃, -NO₂, -OH, -OC₁-C₆-alkyl, -NH₂, C(=O) or C₁-C₆-alkyl,

Q is a valence bond, C₁-C₆-alkylene, -C₁-C₆-alkyl-O-, -C₁-C₆-alkyl-NH-, -NH-C₁-C₆-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C₁-C₆-alkyl, -C(=O)-, or -C₁-C₆-alkyl-C(=O)-N(R⁴⁷)- wherein the
10 alkyl moieties are optionally substituted with one or more substituents independently selected from R⁴⁸,

R⁴⁷ and R⁴⁸ are independently selected from hydrogen, C₁-C₆-alkyl, aryl optionally substituted with one or more R⁴⁹,

15 R⁴⁹ is independently selected from halogen and -COOH,

T is

20 •hydrogen,
•C₁-C₆-alkyl, C₂-C₆-alkenyl , C₂-C₆-alkynyl, C₁-C₆-alkyloxy-carbonyl, wherein the alkyl, alkenyl and alkynyl moieties are optionally substituted with one or more substituents independently selected from R⁵⁰,
25 •aryl, aryloxy, aryloxy-carbonyl, aryl-C₁-C₆-alkyl, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl-, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-alkenyl, heteroaryl-C₂-C₆-alkynyl,

wherein any alkyl, alkenyl , alkynyl, aryl and heteroaryl moiety is optionally substituted with one or more substituents independently selected from R⁵⁰,

30 R⁵⁰ is C₁-C₆-alkyl, C₁-C₆-alkoxy, aryl, aryloxy, aryl-C₁-C₆-alkoxy, -C(=O)-NH-C₁-C₆-alkyl-aryl, heteroaryl, heteroaryl-C₁-C₆-alkoxy, -C₁-C₆-alkyl-COOH, -O-C₁-C₆-alkyl-COOH, -S(O)₂R⁵¹, -C₂-C₆-alkenyl-COOH, -OR⁵¹, -NO₂, halogen, -COOH, -CF₃, -CN, =O, -N(R⁵¹R⁵²), wherein the aryl or heteroaryl moieties are optionally substituted with one or more R⁵³,

R⁵¹ and R⁵² are independently selected from hydrogen and C₁-C₆-alkyl,
R⁵³ is independently selected from C₁-C₆-alkyl, C₁-C₆-alkoxy, -C₁-C₆-alkyl-COOH, -C₂-C₆-alkenyl-COOH, -OR⁵¹, -NO₂, halogen, -COOH, -CF₃, -CN, or -N(R⁵¹R⁵²),

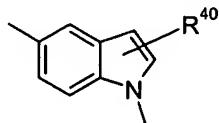
- 5 or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.
In another embodiment the invention provides a pharmaceutical composition wherein K is a valence bond, C₁-C₆-alkylene, -NH-C(=O)-U-, -C₁-C₆-alkyl-S-, -C₁-C₆-alkyl-O-, or -C(=O)-, wherein any C₁-C₆-alkyl moiety is optionally substituted with R³⁸.
- 10 In another embodiment the invention provides a pharmaceutical composition wherein K is a valence bond, C₁-C₆-alkylene, -NH-C(=O)-U-, -C₁-C₆-alkyl-S-, or -C₁-C₆-alkyl-O, wherein any C₁-C₆-alkyl moiety is optionally substituted with R³⁸.
In another embodiment the invention provides a pharmaceutical composition wherein K is a valence bond, C₁-C₆-alkylene, or -NH-C(=O)-U, wherein any C₁-C₆-alkyl moiety is optionally substituted with R³⁸.
- 15 In another embodiment the invention provides a pharmaceutical composition wherein K is a valence bond or C₁-C₆-alkylene, wherein any C₁-C₆-alkyl moiety is optionally substituted with R³⁸.
In another embodiment the invention provides a pharmaceutical composition wherein K is a valence bond or -NH-C(=O)-U.
- 20 In another embodiment the invention provides a pharmaceutical composition wherein K is a valence bond.
In another embodiment the invention provides a pharmaceutical composition wherein U is a valence bond or -C₁-C₆-alkyl-O-.
- 25 In another embodiment the invention provides a pharmaceutical composition wherein U is a valence bond.
In another embodiment the invention provides a pharmaceutical composition wherein M is arylene or heteroarylene, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R⁴⁰.
- 30 In another embodiment the invention provides a pharmaceutical composition wherein M is ArG1 or Het1, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R⁴⁰.
In another embodiment the invention provides a pharmaceutical composition wherein M is ArG1 or Het2, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R⁴⁰.
- 35

In another embodiment the invention provides a pharmaceutical composition wherein M is ArG1 or Het3, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R⁴⁰.

5 In another embodiment the invention provides a pharmaceutical composition wherein M is phenylene optionally substituted with one or more substituents independently selected from R⁴⁰.

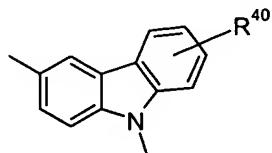
In another embodiment the invention provides a pharmaceutical composition wherein M is indolylene optionally substituted with one or more substituents independently selected from R⁴⁰.

10 In another embodiment the invention provides a pharmaceutical composition wherein M is



In another embodiment the invention provides a pharmaceutical composition wherein M is carbazolylene optionally substituted with one or more substituents independently selected from R⁴⁰.

15 In another embodiment the invention provides a pharmaceutical composition wherein M is



In another embodiment the invention provides a pharmaceutical composition wherein R⁴⁰ is selected from

20 • hydrogen, halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR⁴¹, -NR⁴¹R⁴², -SR⁴¹, -S(O)₂R⁴¹, -NR⁴¹C(O)R⁴², -OC₁-C₆-alkyl-C(O)NR⁴¹R⁴², -C₂-C₆-alkenyl-C(=O)OR⁴¹, -C(O)OR⁴¹, =O, -NH-C(=O)-O-C₁-C₆-alkyl, or -NH-C(=O)-C(=O)-O-C₁-C₆-alkyl,

C₁-C₆-alkyl or C₂-C₆- alkenyl which may each optionally be substituted with one or more substituents independently selected from R⁴³,

25

- aryl, aryloxy, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, or heteroaryl-C₂-C₆-alkenyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R⁴⁴.

In another embodiment the invention provides a pharmaceutical composition wherein R⁴⁰ is

30 selected from

- hydrogen, halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR⁴¹, -NR⁴¹R⁴², -SR⁴¹, -S(O)₂R⁴¹, -NR⁴¹C(O)R⁴², -OC₁-C₆-alkyl-C(O)NR⁴¹R⁴², -C₂-C₆-alkenyl-C(=O)OR⁴¹, -C(O)OR⁴¹, =O, -NH-C(=O)-O-C₁-C₆-alkyl, or -NH-C(=O)-C(=O)-O-C₁-C₆-alkyl,

5 C₁-C₆-alkyl or C₂-C₆- alkenyl which may each optionally be substituted with one or more substituents independently selected from R⁴³,

10 • ArG1, ArG1-O-, ArG1-C₁-C₆-alkoxy, ArG1-C₁-C₆-alkyl, ArG1-C₂-C₆-alkenyl, Het3, Het3-C₁-C₆-alkyl, or Het3-C₂-C₆-alkenyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R⁴⁴.

In another embodiment the invention provides a pharmaceutical composition wherein R⁴⁰ is selected from

- hydrogen, halogen, -CF₃, -NO₂, -OR⁴¹, -NR⁴¹R⁴², -C(O)OR⁴¹, =O, or -NR⁴¹C(O)R⁴²,
- C₁-C₆-alkyl,
- ArG1.

15 In another embodiment the invention provides a pharmaceutical composition wherein R⁴⁰ is selected from

- Halogen, -NO₂, -OR⁴¹, -NR⁴¹R⁴², -C(O)OR⁴¹, or -NR⁴¹C(O)R⁴²,
- Methyl,
- Phenyl.

20 In another embodiment the invention provides a pharmaceutical composition wherein R⁴¹ and R⁴² are independently selected from hydrogen, C₁-C₆-alkyl, or aryl, wherein the aryl moieties may optionally be substituted with halogen or -COOH.

25 In another embodiment the invention provides a pharmaceutical composition wherein R⁴¹ and R⁴² are independently selected from hydrogen, methyl, ethyl, or phenyl, wherein the phenyl moieties may optionally be substituted with halogen or -COOH.

30 In another embodiment the invention provides a pharmaceutical composition wherein Q is a valence bond, C₁-C₆-alkylene, -C₁-C₆-alkyl-O-, -C₁-C₆-alkyl-NH-, -NH-C₁-C₆-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C₁-C₆-alkyl, -C(=O)-, or -C₁-C₆-alkyl-C(=O)-N(R⁴⁷)- wherein the alkyl moieties are optionally substituted with one or more substituents independently selected from R⁴⁸.

35 In another embodiment the invention provides a pharmaceutical composition wherein Q is a valence bond, -CH₂-, -CH₂-CH₂-, -CH₂-O-, -CH₂-CH₂-O-, -CH₂-NH-, -CH₂-CH₂-NH-, -NH-CH₂-, -NH-CH₂-CH₂-, -NH-C(=O)-, -C(=O)-NH-, -O-CH₂-, -O-CH₂-CH₂-, or -C(=O)-.

In another embodiment the invention provides a pharmaceutical composition wherein R⁴⁷ and R⁴⁸ are independently selected from hydrogen, methyl and phenyl.

In another embodiment the invention provides a pharmaceutical composition wherein T is

- hydrogen,
- 5 • C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R⁵⁰,
- aryl, aryl-C₁-C₆-alkyl, heteroaryl, wherein the alkyl, aryl and heteroaryl moieties are optionally substituted with one or more substituents independently selected from R⁵⁰.

In another embodiment the invention provides a pharmaceutical composition wherein T is

- 10
 - hydrogen,
 - C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R⁵⁰,
 - ArG1, ArG1-C₁-C₆-alkyl, Het3, wherein the alkyl, aryl and heteroaryl moieties are optionally substituted with one or more substituents independently selected from R⁵⁰.

15

In another embodiment the invention provides a pharmaceutical composition wherein T is

- hydrogen,
- C₁-C₆-alkyl, optionally substituted with one or more substituents independently selected from R⁵⁰,
- 20 • phenyl, phenyl-C₁-C₆-alkyl, wherein the alkyl and phenyl moieties are optionally substituted with one or more substituents independently selected from R⁵⁰.

In another embodiment the invention provides a pharmaceutical composition wherein R⁵⁰ is C₁-C₆-alkyl, C₁-C₆-alkoxy, aryl, aryloxy, aryl-C₁-C₆-alkoxy, -C(=O)-NH-C₁-C₆-alkyl-aryl, 25 heteroaryl, -C₁-C₆-alkyl-COOH, -O-C₁-C₆-alkyl-COOH, -S(O)₂R⁵¹, -C₂-C₆-alkenyl-COOH, -OR⁵¹, -NO₂, halogen, -COOH, -CF₃, -CN, =O, -N(R⁵¹R⁵²), wherein the aryl or heteroaryl moieties are optionally substituted with one or more R⁵³.

In another embodiment the invention provides a pharmaceutical composition wherein R⁵⁰ is C₁-C₆-alkyl, C₁-C₆-alkoxy, aryl, aryloxy, aryl-C₁-C₆-alkoxy, -OR⁵¹, -NO₂, halogen, -COOH, 30 -CF₃, wherein any aryl moiety is optionally substituted with one or more R⁵³.

In another embodiment the invention provides a pharmaceutical composition wherein R⁵⁰ is C₁-C₆-alkyl, aryloxy, aryl-C₁-C₆-alkoxy, -OR⁵¹, halogen, -COOH, -CF₃, wherein any aryl moiety is optionally substituted with one or more R⁵³.

In another embodiment the invention provides a pharmaceutical composition wherein R⁵⁰ is C₁-C₆-alkyl, ArG1-O-, ArG1-C₁-C₆-alkoxy, -OR⁵¹, halogen, -COOH, -CF₃, wherein any aryl moiety is optionally substituted with one or more R⁵³.

5 In another embodiment the invention provides a pharmaceutical composition wherein R⁵⁰ is phenyl, methyl or ethyl.

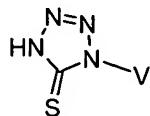
In another embodiment the invention provides a pharmaceutical composition wherein R⁵⁰ is methyl or ethyl.

In another embodiment the invention provides a pharmaceutical composition wherein R⁵¹ is methyl.

10 In another embodiment the invention provides a pharmaceutical composition wherein R⁵³ is C₁-C₆-alkyl, C₁-C₆-alkoxy, -OR⁵¹, halogen, or -CF₃.

In another embodiment the invention provides a pharmaceutical composition wherein the zinc-binding ligand is

15



20 wherein V is C₁-C₆-alkyl, aryl, heteroaryl, aryl-C₁₋₆-alkyl- or aryl-C₂₋₆-alkenyl-, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R⁵⁴, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R⁵⁵,

R⁵⁴ is independently selected from halogen, -CN, -CF₃, -OCF₃, aryl, -COOH and -NH₂,

R⁵⁵ is independently selected from

25 •hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -S(O)₂CF₃, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR⁵⁶, -NR⁵⁶R⁵⁷, -SR⁵⁶, -NR⁵⁶S(O)₂R⁵⁷, -S(O)₂NR⁵⁶R⁵⁷, -S(O)NR⁵⁶R⁵⁷, -S(O)R⁵⁶, -S(O)₂R⁵⁶, -OS(O)₂R⁵⁶, -C(O)NR⁵⁶R⁵⁷, -OC(O)NR⁵⁶R⁵⁷, -NR⁵⁶C(O)R⁵⁷, -CH₂C(O)NR⁵⁶R⁵⁷, -OC₁-C₆-alkyl-C(O)NR⁵⁶R⁵⁷, -CH₂OR⁵⁶, -CH₂OC(O)R⁵⁶, -CH₂NR⁵⁶R⁵⁷, -OC(O)R⁵⁶, -OC₁-C₈-alkyl-C(O)OR⁵⁶, -OC₁-C₆-alkyl-OR⁵⁶, -SC₁-C₆-alkyl-C(O)OR⁵⁶, -C₂-C₆-alkenyl-C(=O)OR⁵⁶, -NR⁵⁶-C(=O)-C₁-C₆-alkenyl-C(=O)OR⁵⁶, -NR⁵⁶-C(=O)-C₁-C₆-alkenyl-C(=O)OR⁵⁶, -C(O)OR⁵⁶, or -C₂-C₆-alkenyl-C(=O)R⁵⁶,

- C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl,

which may optionally be substituted with one or more substituents selected from R⁵⁸,

- 5
 - aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, aroyl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-alkenyl or heteroaryl-C₂-C₆-alkynyl,

10 of which the cyclic moieties optionally may be substituted with one or more substituents selected from R⁵⁹,

R⁵⁶ and R⁵⁷ are independently selected from hydrogen, OH, CF₃, C₁-C₁₂-alkyl, aryl-C₁-C₆-alkyl, -C(=O)-C₁-C₆-alkyl or aryl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R⁶⁰, and the aryl groups may 15 optionally be substituted with one or more substituents independently selected from R⁶¹; R⁵⁶ and R⁵⁷ when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

20

R⁵⁸ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OR⁵⁶, and -NR⁵⁶R⁵⁷,

R⁵⁹ is independently selected from halogen, -C(O)OR⁵⁶, -CH₂C(O)OR⁵⁶, -CH₂OR⁵⁶, -CN, -CF₃, -OCF₃, -NO₂, -OR⁵⁶, -NR⁵⁶R⁵⁷ and C₁-C₆-alkyl,

25

R⁶⁰ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OC₁-C₆-alkyl, -C(O)OC₁-C₆-alkyl, -C(=O)-R⁶², -COOH and -NH₂,

30 R⁶¹ is independently selected from halogen, -C(O)OC₁-C₆-alkyl, -COOH, -CN, -CF₃, -OCF₃, -NO₂, -OH, -OC₁-C₆-alkyl, -NH₂, C(=O) or C₁-C₆-alkyl,

R⁶² is C₁-C₆-alkyl, aryl optionally substituted with one or more substituents independently selected from halogen, or heteroaryl optionally substituted with one or more C₁-C₆-alkyl independently,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

- In another embodiment the invention provides a pharmaceutical composition wherein V is
5 aryl, heteroaryl, or aryl-C₁₋₆-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected R⁵⁴, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R⁵⁵.
- In another embodiment the invention provides a pharmaceutical composition wherein V is
10 aryl, Het1, or aryl-C₁₋₆-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R⁵⁴, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R⁵⁵.
- In another embodiment the invention provides a pharmaceutical composition wherein V is
15 aryl, Het2, or aryl-C₁₋₆-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R⁵⁴, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R⁵⁵.
- In another embodiment the invention provides a pharmaceutical composition wherein V is
20 aryl, Het3, or aryl-C₁₋₆-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R⁵⁴, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R⁵⁵.
- In another embodiment the invention provides a pharmaceutical composition wherein V is
25 aryl optionally substituted with one or more substituents independently selected from R⁵⁵.
- In another embodiment the invention provides a pharmaceutical composition wherein V is
30 ArG1 optionally substituted with one or more substituents independently selected from R⁵⁵.
- In another embodiment the invention provides a pharmaceutical composition wherein V is
phenyl, naphthyl or anthranyl optionally substituted with one or more substituents independently selected from R⁵⁵.
In another embodiment the invention provides a pharmaceutical composition wherein V is
phenyl optionally substituted with one or more substituents independently selected from R⁵⁵.
In another embodiment the invention provides a pharmaceutical composition wherein R⁵⁵ is
independently selected from
• halogen, C₁-C₆-alkyl, -CN, -OCF₃, -CF₃, -NO₂, -OR⁵⁶, -NR⁵⁶R⁵⁷, -NR⁵⁶C(O)R⁵⁷
-SR⁵⁶, -OC₁-C₈-alkyl-C(O)OR⁵⁶, or -C(O)OR⁵⁶,
• C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R⁵⁸
35 • aryl, aryl-C₁-C₆-alkyl, heteroaryl, or heteroaryl-C₁-C₆-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents independently selected from R⁵⁹.

In another embodiment the invention provides a pharmaceutical composition wherein R⁵⁵ is independently selected from

- 5 • halogen, C₁-C₆-alkyl, -CN, -OCF₃, -CF₃, -NO₂, -OR⁵⁶, -NR⁵⁶R⁵⁷, -NR⁵⁶C(O)R⁵⁷
-SR⁵⁶, -OC₁-C₈-alkyl-C(O)OR⁵⁶, or -C(O)OR⁵⁶
- C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R⁵⁸
- ArG1, ArG1-C₁-C₆-alkyl, Het3, or Het3-C₁-C₆-alkyl

10 of which the cyclic moieties optionally may be substituted with one or more substituents independently selected from R⁵⁹.

In another embodiment the invention provides a pharmaceutical composition wherein R⁵⁵ is independently selected from halogen, -OR⁵⁶, -NR⁵⁶R⁵⁷, -C(O)OR⁵⁶, -OC₁-C₈-alkyl-C(O)OR⁵⁶,
15 -NR⁵⁶C(O)R⁵⁷ or C₁-C₆-alkyl.

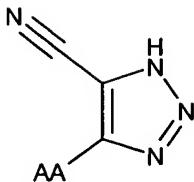
In another embodiment the invention provides a pharmaceutical composition wherein R⁵⁵ is independently selected from halogen, -OR⁵⁶, -NR⁵⁶R⁵⁷, -C(O)OR⁵⁶, -OC₁-C₈-alkyl-C(O)OR⁵⁶,
-NR⁵⁶C(O)R⁵⁷, methyl or ethyl.

20 In another embodiment the invention provides a pharmaceutical composition wherein R⁵⁶ and R⁵⁷ are independently selected from hydrogen, CF₃, C₁-C₁₂-alkyl, or -C(=O)-C₁-C₆-alkyl; R⁵⁶ and R⁵⁷ when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

25 In another embodiment the invention provides a pharmaceutical composition wherein R⁵⁶ and R⁵⁷ are independently selected from hydrogen or C₁-C₁₂-alkyl, R⁵⁶ and R⁵⁷ when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

30 In another embodiment the invention provides a pharmaceutical composition wherein R⁵⁶ and R⁵⁷ are independently selected from hydrogen or methyl, ethyl, propyl butyl, R⁵⁶ and R⁵⁷ when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

In another embodiment the invention provides a pharmaceutical composition 1 wherein the zinc-binding ligand is



wherein AA is C₁-C₆-alkyl, aryl, heteroaryl, aryl-C₁₋₆-alkyl- or aryl-C₂₋₆-alkenyl-, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected

5 from R⁶³, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R⁶⁴,

R⁶³ is independently selected from halogen, -CN, -CF₃, -OCF₃, aryl, -COOH and -NH₂,

10 R⁶⁴ is independently selected from

- hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -S(O)₂CF₃, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR⁶⁵, -NR⁶⁵R⁶⁶, -SR⁶⁵, -NR⁶⁵S(O)₂R⁶⁶, -S(O)₂NR⁶⁵R⁶⁶, -S(O)NR⁶⁵R⁶⁶, -S(O)R⁶⁵, -S(O)₂R⁶⁵, -OS(O)₂R⁶⁵,

15 -C(O)NR⁶⁵R⁶⁶, -OC(O)NR⁶⁵R⁶⁶, -NR⁶⁵C(O)R⁶⁶, -CH₂C(O)NR⁶⁵R⁶⁶, -OC₁-C₆-alkyl-C(O)NR⁶⁵R⁶⁶, -CH₂OR⁶⁵, -CH₂OC(O)R⁶⁵, -CH₂NR⁶⁵R⁶⁶, -OC(O)R⁶⁵, -OC₁-C₆-alkyl-C(O)OR⁶⁵, -OC₁-C₆-alkyl-OR⁶⁵, -SC₁-C₆-alkyl-C(O)OR⁶⁵, -C₂-C₆-alkenyl-C(=O)OR⁶⁵, -NR⁶⁵-C(=O)-C₁-C₆-alkenyl-C(=O)OR⁶⁵, -NR⁶⁵-C(=O)-C₁-C₆-alkenyl-C(=O)OR⁶⁵, or -C₂-C₆-alkenyl-C(=O)R⁶⁵,

20 • C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl, each of which may optionally be substituted with one or more substituents selected from R⁶⁷,

25 • aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, aroyl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-alkenyl or heteroaryl-C₂-C₆-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R⁶⁸,

30 R⁶⁵ and R⁶⁶ are independently selected from hydrogen, OH, CF₃, C₁-C₁₂-alkyl, aryl-C₁-C₆-alkyl, -C(=O)-R⁶⁹, aryl or heteroaryl, wherein the alkyl groups may optionally be substituted

with one or more substituents selected from R⁷⁰, and the aryl and heteroaryl groups may optionally be substituted with one or more substituents independently selected from R⁷¹; R⁶⁵ and R⁶⁶ when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further
5 heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R⁶⁷ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OR⁶⁵, and -NR⁶⁵R⁶⁶,

10 R⁶⁸ is independently selected from halogen, -C(O)OR⁶⁵, -CH₂C(O)OR⁶⁵, -CH₂OR⁶⁵, -CN, -CF₃, -OCF₃, -NO₂, -OR⁶⁵, -NR⁶⁵R⁶⁶ and C₁-C₆-alkyl,

R⁶⁹ is independently selected from C₁-C₆-alkyl, aryl optionally substituted with one or more halogen, or heteroaryl optionally substituted with one or more C₁-C₆-alkyl,

15 R⁷⁰ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OC₁-C₆-alkyl, -C(O)OC₁-C₆-alkyl, -COOH and -NH₂,

20 R⁷¹ is independently selected from halogen, -C(O)OC₁-C₆-alkyl, -COOH, -CN, -CF₃, -OCF₃, -NO₂, -OH, -OC₁-C₆-alkyl, -NH₂, C(=O) or C₁-C₆-alkyl,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

In another embodiment the invention provides a pharmaceutical composition wherein AA is
25 aryl, heteroaryl or aryl-C₁₋₆-alkyl-, wherein the alkyl is optionally substituted with one or more R⁶³, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R⁶⁴.

In another embodiment the invention provides a pharmaceutical composition wherein AA is aryl or heteroaryl optionally substituted with one or more substituents independently selected
30 from R⁶⁴.

In another embodiment the invention provides a pharmaceutical composition wherein AA is ArG1 or Het1 optionally substituted with one or more substituents independently selected from R⁶⁴.

In another embodiment the invention provides a pharmaceutical composition wherein AA is ArG1 or Het2 optionally substituted with one or more substituents independently selected from R⁶⁴.

5 In another embodiment the invention provides a pharmaceutical composition wherein AA is ArG1 or Het3 optionally substituted with one or more substituents independently selected from R⁶⁴.

In another embodiment the invention provides a pharmaceutical composition wherein AA is phenyl, naphtyl, anthryl, carbazolyl, thienyl, pyridyl, or benzodioxyl optionally substituted with one or more substituents independently selected from R⁶⁴.

10 In another embodiment the invention provides a pharmaceutical composition wherein AA is phenyl or naphtyl optionally substituted with one or more substituents independently selected from R⁶⁴.

In another embodiment the invention provides a pharmaceutical composition wherein R⁶⁴ is independently selected from hydrogen, halogen, -CF₃, -OCF₃, -OR⁶⁵, -NR⁶⁵R⁶⁶, C₁-C₆-alkyl ,
15 -OC(O)R⁶⁵, -OC₁-C₆-alkyl-C(O)OR⁶⁵, aryl-C₂-C₆-alkenyl, aryloxy or aryl, wherein C₁-C₆-alkyl is optionally substituted with one or more substituents independently selected from R⁶⁷, and the cyclic moieties optionally are substituted with one or more substituents independently selected from R⁶⁸.

20 In another embodiment the invention provides a pharmaceutical composition wherein R⁶⁴ is independently selected from halogen, -CF₃, -OCF₃, -OR⁶⁵, -NR⁶⁵R⁶⁶, methyl, ethyl, propyl, -OC(O)R⁶⁵, -OCH₂-C(O)OR⁶⁵, -OCH₂-CH₂-C(O)OR⁶⁵, phenoxy optionally substituted with one or more substituents independently selected from R⁶⁸.

In another embodiment the invention provides a pharmaceutical composition wherein R⁶⁵ and R⁶⁶ are independently selected from hydrogen, CF₃, C₁-C₁₂-alkyl, aryl, or heteroaryl optionally 25 substituted with one or more substituents independently selected from R⁷¹.

In another embodiment the invention provides a pharmaceutical composition wherein R⁶⁵ and R⁶⁶ are independently hydrogen, C₁-C₁₂-alkyl, aryl, or heteroaryl optionally substituted with one or more substituents independently selected from R⁷¹.

30 In another embodiment the invention provides a pharmaceutical composition wherein R⁶⁵ and R⁶⁶ are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het1 optionally substituted with one or more substituents independently selected from R⁷¹.

In another embodiment the invention provides a pharmaceutical composition wherein R⁶⁵ and R⁶⁶ are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het2 optionally substituted with one or more substituents independently selected from R⁷¹.

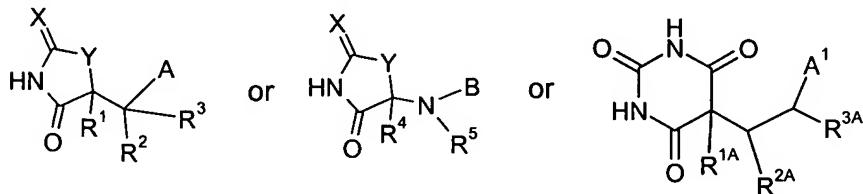
In another embodiment the invention provides a pharmaceutical composition wherein R⁶⁵ and R⁶⁶ are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het3 optionally substituted with one or more substituents independently selected from R⁷¹.

- 5 In another embodiment the invention provides a pharmaceutical composition wherein R⁶⁵ and R⁶⁶ are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, phenyl, naphtyl, thiadiazolyl optionally substituted with one or more R⁷¹ independently; or isoxazolyl optionally substituted with one or more substituents independently selected from R⁷¹.
- 10 In another embodiment the invention provides a pharmaceutical composition wherein R⁷¹ is halogen or C₁-C₆-alkyl.
- 15 In another embodiment the invention provides a pharmaceutical composition wherein R⁷¹ is halogen or methyl.

In another aspect the invention provides a pharmaceutical composition comprising insulin and a zinc-binding ligand which reversibly binds to a His^{B10} Zn²⁺ site of an insulin hexamer, wherein the ligand is selected from the group consisting of benzotriazoles, 3-hydroxy 2-naphthoic acids, salicylic acids, tetrazoles, thiazolidinediones, 5-mercaptotetrazoles, or 4-cyano-1,2,3-triazoles, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

20

In one embodiment hereof the zinc-binding ligand is



wherein

X is =O, =S or =NH

25 Y is -S-, -O- or -NH-

R¹, R^{1A} and R⁴ are independently selected from hydrogen or C₁-C₆-alkyl,

R² and R^{2A} are hydrogen or C₁-C₆-alkyl or aryl, R¹ and R² may optionally be combined to form a double bond, R^{1A} and R^{2A} may optionally be combined to form a double bond,

R³, R^{3A} and R⁵ are independently selected from hydrogen, halogen, aryl optionally substituted with one or more substituents independently selected from R¹⁶, C₁-C₆-alkyl, or -C(O)NR¹¹R¹²,

- 5 A, A¹ and B are independently selected from C₁-C₆-alkyl, aryl, aryl-C₁-C₆-alkyl, -NR¹¹-aryl, aryl-C₂-C₆-alkenyl or heteroaryl, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R⁶ and the aryl or heteroaryl is optionally substituted with up to four substituents R⁷, R⁸, R⁹, and R¹⁰,
A and R³ may be connected through one or two valence bonds, B and R⁵ may be connected
10 through one or two valence bonds,
R⁶ is independently selected from halogen, -CN, -CF₃, -OCF₃, aryl, -COOH and -NH₂,
R⁷, R⁸, R⁹ and R¹⁰ are independently selected from

- 15 •hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃,
-OCF₂CHF₂, -S(O)₂CF₃, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR¹¹, -NR¹¹R¹², -SR¹¹,
-NR¹¹S(O)₂R¹², -S(O)₂NR¹¹R¹², -S(O)NR¹¹R¹², -S(O)R¹¹, -S(O)₂R¹¹, -OS(O)₂R¹¹,
-C(O)NR¹¹R¹², -OC(O)NR¹¹R¹², -NR¹¹C(O)R¹², -CH₂C(O)NR¹¹R¹²,
-OC₁-C₆-alkyl-C(O)NR¹¹R¹², -CH₂OR¹¹, -CH₂OC(O)R¹¹, -CH₂NR¹¹R¹², -OC(O)R¹¹,
-OC₁-C₁₅-alkyl-C(O)OR¹¹, -OC₁-C₆-alkyl-OR¹¹, -SC₁-C₆-alkyl-C(O)OR¹¹,
20 -C₂-C₆-alkenyl-C(=O)OR¹¹, -NR¹¹-C(=O)-C₁-C₆-alkyl-C(=O)OR¹¹,
-NR¹¹-C(=O)-C₁-C₆-alkenyl-C(=O)OR¹¹, -C(O)OR¹¹, C(O)R¹¹, or -C₂-C₆-alkenyl-
C(=O)R¹¹, =O, or -C₂-C₆-alkenyl-C(=O)-NR¹¹R¹²,
25 •C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl, each of which may optionally be
substituted with one or more substituents independently selected from R¹³,
30 •aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl,
aryl-C₂-C₆-alkenyl, aroyl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-
C₆-alkyl, heteroaryl-C₂-C₆-alkenyl, heteroaryl-C₂-C₆-alkynyl, or C₃-C₆ cycloalkyl,
of which each cyclic moiety may optionally be substituted with one or more
substituents independently selected from R¹⁴,
R¹¹ and R¹² are independently selected from hydrogen, OH, C₁-C₂₀-alkyl, aryl-C₁-C₆-alkyl or
35 aryl, wherein the alkyl groups may optionally be substituted with one or more substituents

independently selected from R¹⁵, and the aryl groups may optionally be substituted one or more substituents independently selected from R¹⁶; R¹¹ and R¹² when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen,

5 oxygen and sulphur, and optionally containing one or two double bonds,

R¹³ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OR¹¹, -C(O)OR¹¹ , -NR¹¹R¹², and -C(O)NR¹¹R¹²,

10 R¹⁴ is independently selected from halogen, -C(O)OR¹¹, -CH₂C(O)OR¹¹, -CH₂OR¹¹, -CN, -CF₃, -OCF₃, -NO₂, -OR¹¹, -NR¹¹R¹², -NR¹¹C(O)R¹¹, -S(O)₂R¹¹, aryl and C₁-C₆-alkyl,

R¹⁵ is independently selected from halogen, -CN, -CF₃, =O, -OCF₃, -OC₁-C₆-alkyl, -C(O)OC₁-C₆-alkyl, -COOH and -NH₂,

15

R¹⁶ is independently selected from halogen, -C(O)OC₁-C₆-alkyl, -COOH, -CN, -CF₃, -OCF₃, -NO₂, -OH, -OC₁-C₆-alkyl, -NH₂, C(=O) or C₁-C₆-alkyl, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

20

In another embodiment hereof X is =O or =S.

In another embodiment hereof X is =O.

In another embodiment hereof X is =S.

In another embodiment hereof Y is -O- or -S-.

25 In another embodiment hereof Y is -O-.

In another embodiment hereof Y is -NH-.

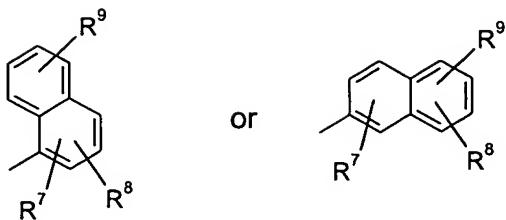
In another embodiment hereof Y is -S-.

In another embodiment hereof A is aryl optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

30 In another embodiment hereof A is selected from ArG1 optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

In another embodiment hereof A is phenyl or naphtyl optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

In another embodiment hereof A is



In another embodiment hereof A is phenyl.

In another embodiment hereof A is heteroaryl optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

- 5 In another embodiment hereof A is selected from Het1 optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

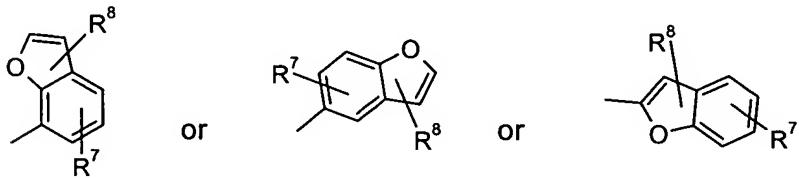
In another embodiment hereof A is selected from Het2 optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

- 10 In another embodiment hereof A is selected from Het3 optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

In another embodiment hereof A is selected from the group consisting of indolyl, benzofuranyl, quinolyl, furyl, thieryl, or pyrrolyl, wherein each heteroaryl may optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

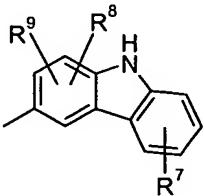
- 15 In another embodiment hereof A is benzofuranyl optionally substituted with up to four substituents R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

In another embodiment hereof A is



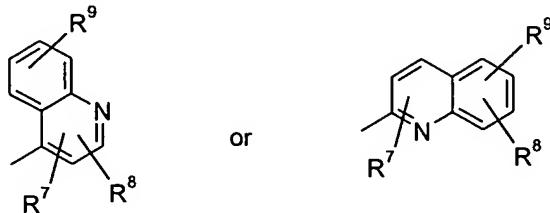
- 20 In another embodiment hereof A is carbazolyl optionally substituted with up to four substituents R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

In another embodiment hereof A is



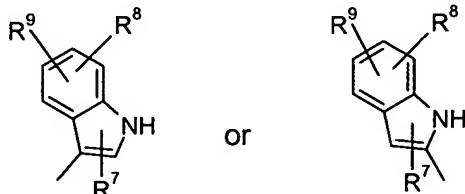
In another embodiment hereof A is quinolyl optionally substituted with up to four substituents R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

In another embodiment hereof A is



In another embodiment hereof A is indolyl optionally substituted with up to four substituents R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

5 In another embodiment hereof A is



In another embodiment hereof R¹ is hydrogen.

In another embodiment hereof R² is hydrogen.

In another embodiment hereof R¹ and R² are combined to form a double bond.

10 In another embodiment hereof R³ is C₁-C₆-alkyl, halogen, or C(O)NR¹⁶R¹⁷.

In another embodiment hereof R³ is C₁-C₆-alkyl or C(O)NR¹⁶R¹⁷.

In another embodiment hereof R³ is methyl.

In another embodiment hereof B is phenyl optionally substituted with up to four substituents, R⁷, R⁸, R⁹, and R¹⁰ which may be the same or different.

15 In another embodiment hereof R⁴ is hydrogen.

In another embodiment hereof R⁵ is hydrogen.

In another embodiment hereof R⁶ is aryl.

In another embodiment hereof R⁶ is phenyl.

In another embodiment hereof R⁷, R⁸, R⁹ and R¹⁰ are independently selected from

20

- hydrogen, halogen, -NO₂, -OR¹¹, -NR¹¹R¹², -SR¹¹, -NR¹¹S(O)₂R¹², -S(O)₂NR¹¹R¹², -S(O)NR¹¹R¹², -S(O)R¹¹, -S(O)₂R¹¹, -OS(O)₂R¹¹, -NR¹¹C(O)R¹², -CH₂OR¹¹, -CH₂OC(O)R¹¹, -CH₂NR¹¹R¹², -OC(O)R¹¹, -OC₁-C₆-alkyl-C(O)OR¹¹, -OC₁-C₆-alkyl-C(O)NR¹¹R¹², -OC₁-C₆-alkyl-OR¹¹, -SC₁-C₆-alkyl-C(O)OR¹¹, -C₂-C₆-alkenyl-C(=O)OR¹¹, -C(O)OR¹¹, or -C₂-C₆-alkenyl-C(=O)R¹¹,

25

• C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl, which may each optionally be substituted with one or more substituents independently selected from R¹³

5 • aryl, aryloxy, aroyl, arylsulfanyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, aroyl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, wherein each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R¹⁴

In another embodiment hereof R⁷, R⁸, R⁹ and R¹⁰ are independently selected from

10

• hydrogen, halogen, -NO₂, -OR¹¹, -NR¹¹R¹², -SR¹¹, -S(O)₂R¹¹, -OS(O)₂R¹¹, -CH₂OC(O)R¹¹, -OC(O)R¹¹, -OC₁-C₆-alkyl-C(O)OR¹¹, -OC₁-C₆-alkyl-OR¹¹, -SC₁-C₆-alkyl-C(O)OR¹¹, -C(O)OR¹¹, or -C₂-C₆-alkenyl-C(=O)R¹¹,

15

• C₁-C₆-alkyl or C₁-C₆-alkenyl which may each optionally be substituted with one or more substituents independently selected from R¹³

• aryl, aryloxy, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, heteroaryl,

20

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R¹⁴

In another embodiment hereof R⁷, R⁸, R⁹ and R¹⁰ are independently selected from

25

• hydrogen, halogen, -NO₂, -OR¹¹, -NR¹¹R¹², -SR¹¹, -S(O)₂R¹¹, -OS(O)₂R¹¹, -CH₂OC(O)R¹¹, -OC(O)R¹¹, -OC₁-C₆-alkyl-C(O)OR¹¹, -OC₁-C₆-alkyl-OR¹¹, -SC₁-C₆-alkyl-C(O)OR¹¹, -C(O)OR¹¹, or -C₂-C₆-alkenyl-C(=O)R¹¹,

30

• C₁-C₆-alkyl or C₁-C₆- which may each optionally be substituted with one or more substituents independently selected from R¹³

• aryl, aryloxy, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, heteroaryl,

35

of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R¹⁴.

In another embodiment hereof R⁷, R⁸, R⁹ and R¹⁰ are independently selected from

- hydrogen, halogen, -OR¹¹, -OC₁-C₆-alkyl-C(O)OR¹¹, or -C(O)OR¹¹,

5 • C₁-C₆-alkyl which may each optionally be substituted with one or more substituents independently selected from R¹³

- aryl, aryloxy, aryl-C₁-C₆-alkoxy,

10 of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R¹⁴.

In another embodiment hereof R⁷, R⁸, R⁹ and R¹⁰ are independently selected from

- hydrogen, halogen, -OR¹¹, -OC₁-C₆-alkyl-C(O)OR¹¹, or -C(O)OR¹¹,

15 • C₁-C₆-alkyl which may each optionally be substituted with one or more substituents independently selected from R¹³

- ArG1, ArG1oxy, ArG1-C₁-C₆-alkoxy,

20 of which each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R¹⁴.

In another embodiment hereof R⁷, R⁸, R⁹ and R¹⁰ are independently selected from

- hydrogen, halogen, -OR¹¹, -OC₁-C₆-alkyl-C(O)OR¹¹, or -C(O)OR¹¹,

25 • C₁-C₆-alkyl which may optionally be substituted with one or more substituents independently selected from R¹³

30 • phenyl, phenoxy, phenyl-C₁-C₆-alkoxy, wherein each of the cyclic moieties optionally may be substituted with one or more substituents independently selected from R¹⁴.

In another embodiment hereof R¹¹ and R¹² are independently selected from hydrogen, C₁-C₂₀-alkyl, aryl or aryl-C₁-C₆-alkyl, wherein the alkyl groups may optionally be substituted with

35 one or more substituents independently selected from R¹⁵, and the aryl groups may

optionally be substituted one or more substituents independently selected from R¹⁶, R¹¹ and R¹² when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or

5 two double bonds.

In another embodiment hereof R¹¹ and R¹² are independently selected from hydrogen, C₁-C₂₀-alkyl, aryl or aryl-C₁-C₆-alkyl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R¹⁵, and the aryl groups may optionally be substituted one or more substituents independently selected from R¹⁶.

10 In another embodiment hereof R¹¹ and R¹² are independently selected from phenyl or phenyl-C₁-C₆-alkyl.

In another embodiment hereof one or both of R¹¹ and R¹² are methyl.

In another embodiment hereof R¹³ is independently selected from halogen, CF₃, OR¹¹ or NR¹¹R¹².

15 In another embodiment hereof R¹³ is independently selected from halogen or OR¹¹.

In another embodiment hereof R¹³ is OR¹¹.

In another embodiment hereof R¹⁴ is independently selected from halogen, -C(O)OR¹¹, -CN, -CF₃, -OR¹¹, S(O)₂R¹¹, and C₁-C₆-alkyl.

20 In another embodiment hereof R¹⁴ is independently selected from halogen, -C(O)OR¹¹, or -OR¹¹.

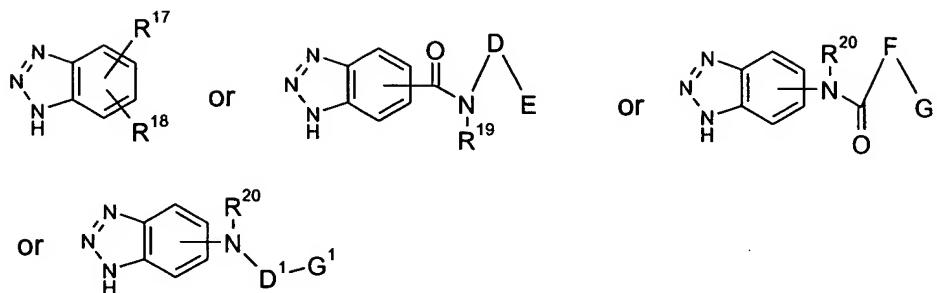
In another embodiment hereof R¹⁵ is independently selected from halogen, -CN, -CF₃, -C(O)OC₁-C₆-alkyl, and -COOH.

In another embodiment hereof R¹⁵ is independently selected from halogen or -C(O)OC₁-C₆-alkyl.

25 In another embodiment hereof R¹⁶ is independently selected from halogen, -C(O)OC₁-C₆-alkyl, -COOH, -NO₂, -OC₁-C₆-alkyl, -NH₂, C(=O) or C₁-C₆-alkyl.

In another embodiment hereof R¹⁶ is independently selected from halogen, -C(O)OC₁-C₆-alkyl, -COOH, -NO₂, or C₁-C₆-alkyl.

In another embodiment hereof the zinc-binding ligand is



wherein

R^{19} is hydrogen or $C_1\text{-}C_6$ -alkyl,

5 R^{20} is hydrogen or $C_1\text{-}C_6$ -alkyl,

D, D^1 and F are a valence bond, $C_1\text{-}C_6$ -alkylene or $C_1\text{-}C_6$ -alkenylene optionally substituted with one or more substituents independently selected from R^{72} ,

10 R^{72} is independently selected from hydroxy, $C_1\text{-}C_6$ -alkyl, or aryl,

E is $C_1\text{-}C_6$ -alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents R^{21} , R^{22} and R^{23} ,

15 G and G^1 are $C_1\text{-}C_6$ -alkyl, aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with up to three substituents R^{24} , R^{25} and R^{26} ,

R^{17} , R^{18} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} and R^{26} are independently selected from

- hydrogen, halogen, -CN, - CH_2CN , - CHF_2 , - CF_3 , - OCF_3 , - $OCHF_2$, - OCH_2CF_3 , - OCF_2CHF_2 , - $S(O)_2CF_3$, - SCF_3 , - NO_2 , =O, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷S(O)₂R²⁸, -S(O)₂NR²⁷R²⁸, -S(O)NR²⁷R²⁸, -S(O)R²⁷, -S(O)₂R²⁷, -C(O)NR²⁷R²⁸, -OC(O)NR²⁷R²⁸, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, - $CH_2C(O)NR^{27}R^{28}$, - $OCH_2C(O)NR^{27}R^{28}$, - CH_2OR^{27} , - $CH_2NR^{27}R^{28}$, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷, -NR²⁷-C(=O)-C₁-C₆-alkyl-C(=O)OR²⁷, -NR²⁷-C(=O)-C₁-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or -C(O)OR²⁷,

- $C_1\text{-}C_6$ -alkyl, $C_2\text{-}C_6$ -alkenyl or $C_2\text{-}C_6$ -alkynyl,

which may optionally be substituted with one or more substituents independently selected from R²⁹,

- 5 • aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-alkenyl or heteroaryl-C₂-C₆-alkynyl,

10 of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰,

10

R²⁷ and R²⁸ are independently selected from hydrogen, C₁-C₆-alkyl, aryl-C₁-C₆-alkyl or aryl, or R²⁷ and R²⁸ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further 15 heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R²⁹ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OR²⁷, and -NR²⁷R²⁸,

20 R³⁰ is independently selected from halogen, -C(O)OR²⁷, -CN, -CF₃, -OCF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸ and C₁-C₆-alkyl, or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

In another embodiment hereof D is a valence bond.

25 In another embodiment hereof D is C₁-C₆-alkylene optionally substituted with one or more hydroxy, C₁-C₆-alkyl, or aryl.

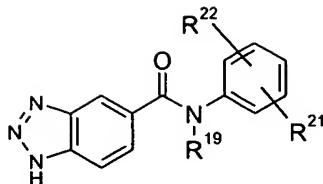
In another embodiment hereof E is aryl or heteroaryl, wherein the aryl or heteroaryl is 30 optionally substituted with up to three substituents independently selected from R²¹, R²² and R²³.

In another embodiment hereof E is aryl optionally substituted with up to three substituents independently selected from R²¹, R²² and R²³.

35 In another embodiment hereof E is selected from ArG1 and optionally substituted with up to three substituents independently selected from R²¹, R²² and R²³.

In another embodiment hereof E is phenyl optionally substituted with up to three substituents independently selected from R²¹, R²² and R²³.

35 In another embodiment hereof the zinc-binding ligand is



In another embodiment hereof R²¹, R²² and R²³ are independently selected from

- 5 •hydrogen, halogen, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCF₂CF₃, -SCF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -C(O)NR²⁷R²⁸, -OC(O)NR²⁷R²⁸, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -CH₂C(O)NR²⁷R²⁸, -OCH₂C(O)NR²⁷R²⁸, -CH₂OR²⁷, -CH₂NR²⁷R²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷, -NR²⁷-C(=O)-C₁-C₆-alkyl-C(=O)OR²⁷, -NR²⁷-C(=O)-C₁-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or -C(O)OR²⁷,
- 10 •C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl,

15 which may optionally be substituted with one or more substituents independently selected from R²⁹

20 •aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-alkenyl or heteroaryl-C₂-C₆-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

25 In another embodiment hereof R²¹, R²² and R²³ are independently selected from

- hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or -C(O)OR²⁷,

•C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R²⁹

5 •aryl, aryloxy, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, heteroaryl, heteroaryl-C₁-C₆-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

10 In another embodiment hereof R²¹, R²² and R²³ are independently selected from

15 •hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸,
-OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷,
-C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or
-C(O)OR²⁷,

20 •methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R²⁹

25 •aryl, aryloxy, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, heteroaryl, heteroaryl-C₁-C₆-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment hereof R²¹, R²² and R²³ are independently selected from

25

•hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸,
-OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷,
-C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or
-C(O)OR²⁷,

30

•methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R²⁹

35 •ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C₁-C₆-alkoxy, ArG1-C₁-C₆-alkyl, Het3, Het3-C₁-C₆-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment hereof R²¹, R²² and R²³ are independently selected from

5 •hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸,
-OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-
C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or
-C(O)OR²⁷,

10 •C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R²⁹

 •phenyl, phenoxy, phenyl-C₁-C₆-alkoxy, phenyl-C₁-C₆-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment hereof R¹⁹ is hydrogen or methyl.

In another embodiment hereof R¹⁹ is hydrogen.

In another embodiment hereof R²⁷ is hydrogen, C₁-C₆-alkyl or aryl.

20 In another embodiment hereof R²⁷ is hydrogen or C₁-C₆-alkyl.

In another embodiment hereof R²⁸ is hydrogen or C₁-C₆-alkyl.

In another embodiment hereof F is a valence bond.

In another embodiment hereof F is C₁-C₆-alkylene optionally substituted with one or more hydroxy, C₁-C₆-alkyl, or aryl.

25 In another embodiment hereof G is C₁-C₆-alkyl or aryl, wherein the aryl is optionally substituted with up to three substituents R²⁴, R²⁵ and R²⁶.

In another embodiment hereof G is C₁-C₆-alkyl or ArG1, wherein the aryl is optionally substituted with up to three substituents R²⁴, R²⁵ and R²⁶.

In another embodiment hereof G is C₁-C₆-alkyl.

30 In another embodiment hereof G is phenyl optionally substituted with up to three substituents R²⁴, R²⁵ and R²⁶.

In another embodiment hereof R²⁴, R²⁵ and R²⁶ are independently selected from

35 •hydrogen, halogen, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -C(O)NR²⁷R²⁸, -OC(O)NR²⁷R²⁸, -NR²⁷C(O)R²⁸,

-NR²⁷C(O)OR²⁸, -CH₂C(O)NR²⁷R²⁸, -OCH₂C(O)NR²⁷R²⁸, -CH₂OR²⁷, -CH₂NR²⁷R²⁸,
-OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-
C(=O)OR²⁷, -NR²⁷-C(=O)-C₁-C₆-alkyl-C(=O)OR²⁷, -NR²⁷-C(=O)-C₁-C₆-
alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or
5 -C(O)OR²⁷,

- C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl,

which may optionally be substituted with one or more substituents independently
10 selected from R²⁹

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-
C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-
alkenyl or heteroaryl-C₂-C₆-alkynyl,

15

of which the cyclic moieties optionally may be substituted with one or more
substituents selected from R³⁰.

In another embodiment hereof R²⁴, R²⁵ and R²⁶ are independently selected from

20

- hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸,
-OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-
C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or
-C(O)OR²⁷,

25

- C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl,

which may optionally be substituted with one or more substituents independently
30 selected from R²⁹

- aryl, aryloxy, aryloxycarbonyl, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-
C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-
alkenyl or heteroaryl-C₂-C₆-alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment hereof R²⁴, R²⁵ and R²⁶ are independently selected from

5

- hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or -C(O)OR²⁷,

10

- C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R²⁹

15

- aryl, aryloxy, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, heteroaryl, heteroaryl-C₁-C₆-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

20 In another embodiment hereof R²¹, R²² and R²³ are independently selected from

25

- hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or -C(O)OR²⁷,

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R²⁹

30

- ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C₁-C₆-alkoxy, ArG1-C₁-C₆-alkyl, Het3, Het3-C₁-C₆-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment hereof R²¹, R²² and R²³ are independently selected from

35

- hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or -C(O)OR²⁷,

5

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R²⁹

10

- ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C₁-C₆-alkoxy, ArG1-C₁-C₆-alkyl, Het3, Het3-C₁-C₆-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment hereof R²¹, R²² and R²³ are independently selected from

15

- hydrogen, halogen, -OCF₃, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -NR²⁷C(O)R²⁸, -NR²⁷C(O)OR²⁸, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, -C₂-C₆-alkenyl-C(=O)OR²⁷, -C(=O)NR²⁷-C₁-C₆-alkyl-C(=O)OR²⁷, -C₁-C₆-alkyl-C(=O)OR²⁷, or -C(O)OR²⁷,

20

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R²⁹

- ArG1, ArG1-O-, ArG1-C₁-C₆-alkoxy, ArG1-C₁-C₆-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

25

In another embodiment hereof R²⁰ is hydrogen or methyl.

In another embodiment hereof R²⁰ is hydrogen.

In another embodiment hereof R²⁷ is hydrogen, C₁-C₆-alkyl or aryl.

In another embodiment hereof R²⁷ is hydrogen or C₁-C₆-alkyl or ArG1.

30

In another embodiment hereof R²⁷ is hydrogen or C₁-C₆-alkyl.

In another embodiment hereof R²⁸ is hydrogen or C₁-C₆-alkyl.

In another embodiment hereof R¹⁷ and R¹⁸ are independently selected from

- hydrogen, halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸, -SR²⁷, -S(O)R²⁷, -S(O)₂R²⁷, -C(O)NR²⁷R²⁸, -CH₂OR²⁷, -OC(O)R²⁷, -OC₁-C₆-alkyl-C(O)OR²⁷, -SC₁-C₆-alkyl-C(O)OR²⁷, or -C(O)OR²⁷,

5 • C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl, optionally substituted with one or more substituents independently selected from R²⁹

- aryl, aryloxy, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, heteroaryl, heteroaryl-C₁-C₆-alkyl,

10 of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment hereof R¹⁷ and R¹⁸ are independently selected from

15 • hydrogen, halogen, -CN, -CF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸, or -C(O)OR²⁷,

- C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R²⁹

20 • aryl, aryloxy, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, heteroaryl, heteroaryl-C₁-C₆-alkyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

25 In another embodiment hereof R¹⁷ and R¹⁸ are independently selected from

- hydrogen, halogen, -CN, -CF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸, or -C(O)OR²⁷
- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R²⁹

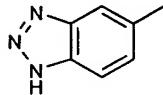
30 • aryl, aryloxy, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, heteroaryl, heteroaryl-C₁-C₆-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.

In another embodiment hereof R¹⁷ and R¹⁸ are independently selected from

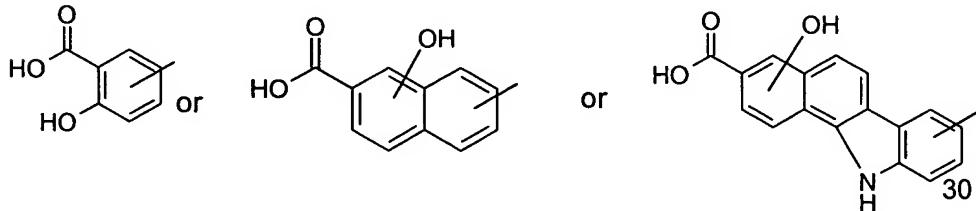
35 • hydrogen, halogen, -CN, -CF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸, or -C(O)OR²⁷

- methyl, ethyl propyl optionally substituted with one or more substituents independently selected from R²⁹
 - ArG1, ArG1-O-, ArG1-C(O)-, ArG1-C₁-C₆-alkoxy, ArG1-C₁-C₆-alkyl, Het3, Het3-C₁-C₆-alkyl
- 5 of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.
- In another embodiment hereof R¹⁷ and R¹⁸ are independently selected from
- hydrogen, halogen, -CN, -CF₃, -NO₂, -OR²⁷, -NR²⁷R²⁸, or -C(O)OR²⁷
 - C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R²⁹
 - phenyl, phenoxy, phenyl-C₁-C₆-alkoxy, phenyl-C₁-C₆-alkyl,
- of which the cyclic moieties optionally may be substituted with one or more substituents selected from R³⁰.
- In another embodiment hereof R²⁷ is hydrogen or C₁-C₆-alkyl.
- 15 In another embodiment hereof R²⁷ is hydrogen, methyl or ethyl.
- In another embodiment hereof R²⁸ is hydrogen or C₁-C₆-alkyl.
- In another embodiment hereof R²⁸ is hydrogen, methyl or ethyl.
- In another embodiment hereof R⁷² is -OH or phenyl.
- 20 In another embodiment hereof the zinc-binding ligand is



In another embodiment hereof the zinc-binding ligand is of the form H-I-J

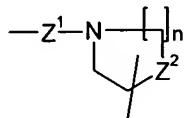
25 wherein H is



wherein the phenyl, naphthalene or benzocarbazole rings are optionally substituted with one or more substituents independently selected from R³¹

I is selected from

- a valence bond,
- $-\text{CH}_2\text{N}(\text{R}^{32})-$ or $-\text{SO}_2\text{N}(\text{R}^{33})-$,



5 • wherein Z^1 is $\text{S}(\text{O})_2$ or CH_2 , Z^2 is $-\text{NH}-$, $-\text{O}-$ or $-\text{S}-$, and n is 1 or 2,

J is

- $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_2\text{-C}_6\text{-alkenyl}$ or $\text{C}_2\text{-C}_6\text{-alkynyl}$, which may each optionally be substituted with one or more substituents selected from R^{34} ,
- 10 • Aryl, aryloxy, aryl-oxycarbonyl-, aroyl, aryl- $\text{C}_1\text{-C}_6\text{-alkoxy-}$, aryl- $\text{C}_1\text{-C}_6\text{-alkyl-}$, aryl- $\text{C}_2\text{-C}_6\text{-alkenyl-}$, aryl- $\text{C}_2\text{-C}_6\text{-alkynyl-}$, heteroaryl, heteroaryl- $\text{C}_1\text{-C}_6\text{-alkyl-}$, heteroaryl- $\text{C}_2\text{-C}_6\text{-alkenyl-}$ or heteroaryl- $\text{C}_2\text{-C}_6\text{-alkynyl-}$, wherein the cyclic moieties are optionally substituted with one or more substituents selected from R^{37} ,
- hydrogen,

15

R^{31} is independently selected from hydrogen, halogen, $-\text{CN}$, $-\text{CH}_2\text{CN}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{CF}_3$, $-\text{OCF}_2\text{CHF}_2$, $-\text{S}(\text{O})_2\text{CF}_3$, $-\text{SCF}_3$, $-\text{NO}_2$, $-\text{OR}^{35}$, $-\text{C}(\text{O})\text{R}^{35}$, $-\text{NR}^{35}\text{R}^{36}$, $-\text{SR}^{35}$, $-\text{NR}^{35}\text{S}(\text{O})_2\text{R}^{36}$, $-\text{S}(\text{O})_2\text{NR}^{35}\text{R}^{36}$, $-\text{S}(\text{O})\text{NR}^{35}\text{R}^{36}$, $-\text{S}(\text{O})\text{R}^{35}$, $-\text{S}(\text{O})_2\text{R}^{35}$, $-\text{C}(\text{O})\text{NR}^{35}\text{R}^{36}$, $-\text{OC}(\text{O})\text{NR}^{35}\text{R}^{36}$, $-\text{NR}^{35}\text{C}(\text{O})\text{R}^{36}$, $-\text{CH}_2\text{C}(\text{O})\text{NR}^{35}\text{R}^{36}$, $-\text{OCH}_2\text{C}(\text{O})\text{NR}^{35}\text{R}^{36}$, $-\text{CH}_2\text{OR}^{35}$, $-\text{CH}_2\text{NR}^{35}\text{R}^{36}$, $-\text{OC}(\text{O})\text{R}^{35}$, $-\text{OC}_1\text{-C}_6\text{-alkyl-C}(\text{O})\text{OR}^{35}$, $-\text{SC}_1\text{-C}_6\text{-alkyl-C}(\text{O})\text{OR}^{35}$, $-\text{C}_2\text{-C}_6\text{-alkenyl-C}(\text{=O})\text{OR}^{35}$, $-\text{NR}^{35}\text{-C}(\text{=O})\text{-C}_1\text{-C}_6\text{-alkyl-C}(\text{=O})\text{OR}^{35}$, $-\text{NR}^{35}\text{-C}(\text{=O})\text{-C}_1\text{-C}_6\text{-alkenyl-C}(\text{=O})\text{OR}^{35}$, $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_1\text{-C}_6\text{-alkanoyl}$ or $-\text{C}(\text{O})\text{OR}^{35}$,

20 R^{32} and R^{33} are independently selected from hydrogen, $\text{C}_1\text{-C}_6\text{-alkyl}$ or $\text{C}_1\text{-C}_6\text{-alkanoyl}$,

25

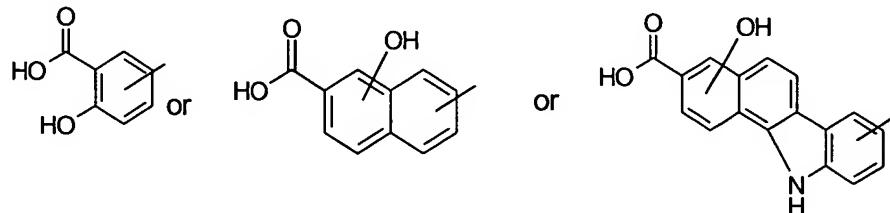
R^{34} is independently selected from halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^{35}$, and $-\text{NR}^{35}\text{R}^{36}$,

30 R^{35} and R^{36} are independently selected from hydrogen, $\text{C}_1\text{-C}_6\text{-alkyl}$, aryl- $\text{C}_1\text{-C}_6\text{-alkyl}$ or aryl, or R^{35} and R^{36} when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

R^{37} is independently selected from halogen, $-C(O)OR^{35}$, $-C(O)H$, $-CN$, $-CF_3$, $-OCF_3$, $-NO_2$, $-OR^{35}$, $-NR^{35}R^{36}$, C_1-C_6 -alkyl or C_1-C_6 -alkanoyl,

- 5 or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

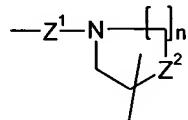
In another embodiment hereof the zinc-binding ligand is of the form H-I-J, wherein H is wherein the phenyl, naphthalene or benzocarbazole rings are optionally substituted with one



- 10 or more substituents independently selected from R^{31} ,

I is selected from

- a valence bond,
- $-CH_2N(R^{32})-$ or $-SO_2N(R^{33})-$,



- 15 • wherein Z^1 is $S(O)_2$ or CH_2 , Z^2 is N - O -or $-S$ -, and n is 1 or 2,

J is

- C_1-C_6 -alkyl, C_2-C_6 -alkenyl or C_2-C_6 -alkynyl, which may each optionally be substituted with one or more substituents selected from R^{34} ,
- 20 • Aryl, aryloxy, aryl-oxygenocarbonyl-, aroyl, aryl- C_1-C_6 -alkoxy-, aryl- C_1-C_6 -alkyl-, aryl- C_2-C_6 -alkenyl-, aryl- C_2-C_6 -alkynyl-, heteroaryl, heteroaryl- C_1-C_6 -alkyl-, heteroaryl- C_2-C_6 -alkenyl- or heteroaryl- C_2-C_6 -alkynyl-, wherein the cyclic moieties are optionally substituted with one or more substituents selected from R^{37} ,
- hydrogen,

25

R^{31} is independently selected from hydrogen, halogen, $-CN$, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{35}$, $-C(O)R^{35}$, $-NR^{35}R^{36}$, $-SR^{35}$,

-NR³⁵S(O)₂R³⁶, -S(O)₂NR³⁵R³⁶, -S(O)NR³⁵R³⁶, -S(O)R³⁵, -S(O)₂R³⁵, -C(O)NR³⁵R³⁶, -OC(O)NR³⁵R³⁶, -NR³⁵C(O)R³⁶, -CH₂C(O)NR³⁵R³⁶, -OCH₂C(O)NR³⁵R³⁶, -CH₂OR³⁵, -CH₂NR³⁵R³⁶, -OC(O)R³⁵, -OC₁-C₆-alkyl-C(O)OR³⁵, -SC₁-C₆-alkyl-C(O)OR³⁵ -C₂-C₆-alkenyl-C(=O)OR³⁵, -NR³⁵-C(=O)-C₁-C₆-alkyl-C(=O)OR³⁵, -NR³⁵-C(=O)-C₁-C₆-alkenyl-C(=O)OR³⁵-, 5 C₁-C₆-alkyl, C₁-C₆-alkanoyl or -C(O)OR³⁵,

R³² and R³³ are independently selected from hydrogen, C₁-C₆-alkyl or C₁-C₆-alkanoyl,

R³⁴ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OR³⁵, and -NR³⁵R³⁶,

10

R³⁵ and R³⁶ are independently selected from hydrogen, C₁-C₆-alkyl, aryl-C₁-C₆-alkyl or aryl, or R³⁵ and R³⁶ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or 15 two double bonds,

R³⁷ is independently selected from halogen, -C(O)OR³⁵, -C(O)H, -CN, -CF₃, -OCF₃, -NO₂, -OR³⁵, -NR³⁵R³⁶, C₁-C₆-alkyl or C₁-C₆-alkanoyl,

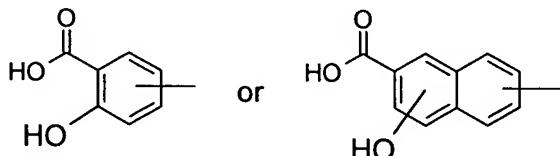
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or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base,

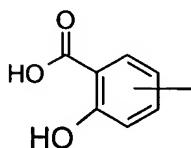
With the proviso that R³¹ and J cannot both be hydrogen.

In another embodiment hereof H is

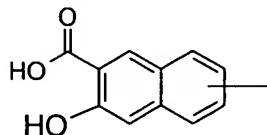
25



In another embodiment hereof H is



In another embodiment hereof H is



In another embodiment hereof I is a valence bond, $-\text{CH}_2\text{N}(\text{R}^{32})-$, or $-\text{SO}_2\text{N}(\text{R}^{33})-$.

In another embodiment hereof I is a valence bond.

5 In another embodiment hereof J is

- hydrogen,
- $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_2\text{-C}_6\text{-alkenyl}$ or $\text{C}_2\text{-C}_6\text{-alkynyl}$,

which may optionally be substituted with one or more substituents selected from halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^{35}$, and $-\text{NR}^{35}\text{R}^{36}$,

10 • aryl, or heteroaryl, wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37} .

In another embodiment hereof J is

- hydrogen,
- aryl or heteroaryl, wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37} .

In another embodiment hereof J is

- hydrogen,
- ArG1 or Het3 , wherein the cyclic moieties are optionally substituted with one or more substituents independently selected from R^{37} .

20 In another embodiment hereof J is

- hydrogen,
- phenyl or naphthyl optionally substituted with one or more substituents independently selected from R^{37} .

In another embodiment hereof J is hydrogen.

25 In another embodiment hereof R^{32} and R^{33} are independently selected from hydrogen or $\text{C}_1\text{-C}_6\text{-alkyl}$.

In another embodiment hereof R^{34} is hydrogen, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{SCF}_3$, $-\text{NO}_2$, $-\text{OR}^{35}$, $-\text{C(O)R}^{35}$, $-\text{NR}^{35}\text{R}^{36}$, $-\text{SR}^{35}$, $-\text{C(O)NR}^{35}\text{R}^{36}$, $-\text{OC(O)NR}^{35}\text{R}^{36}$, $-\text{NR}^{35}\text{C(O)R}^{36}$, $-\text{OC(O)R}^{35}$, $-\text{OC}_1\text{-C}_6\text{-alkyl-C(O)OR}^{35}$, $-\text{SC}_1\text{-C}_6\text{-alkyl-C(O)OR}^{35}$ or $-\text{C(O)OR}^{35}$.

30 In another embodiment hereof R^{34} is hydrogen, halogen, $-\text{CF}_3$, $-\text{NO}_2$, $-\text{OR}^{35}$, $-\text{NR}^{35}\text{R}^{36}$, $-\text{SR}^{35}$, $-\text{NR}^{35}\text{C(O)R}^{36}$, or $-\text{C(O)OR}^{35}$.

In another embodiment hereof R³⁴ is hydrogen, halogen, -CF₃, -NO₂, -OR³⁵, -NR³⁵R³⁶, or -NR³⁵C(O)R³⁶.

In another embodiment hereof R³⁴ is hydrogen, halogen, or -OR³⁵.

In another embodiment hereof R³⁵ and R³⁶ are independently selected from hydrogen, C₁-C₆-alkyl, or aryl.

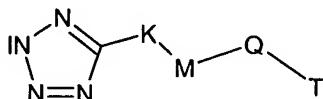
In another embodiment hereof R³⁵ and R³⁶ are independently selected from hydrogen or C₁-C₆-alkyl.

In another embodiment hereof R³⁷ is halogen, -C(O)OR³⁵, -CN, -CF₃, -OR³⁵, -NR³⁵R³⁶, C₁-C₆-alkyl or C₁-C₆-alkanoyl.

10 In another embodiment hereof R³⁷ is halogen, -C(O)OR³⁵, -OR³⁵, -NR³⁵R³⁶, C₁-C₆-alkyl or C₁-C₆-alkanoyl.

In another embodiment hereof R³⁷ is halogen, -C(O)OR³⁵ or -OR³⁵.

In another embodiment hereof the zinc-binding ligand is



15

wherein K is a valence bond, C₁-C₆-alkylene, -NH-C(=O)-U-, -C₁-C₆-alkyl-S-, -C₁-C₆-alkyl-O-, -C(=O)-, or -C(=O)-NH-, wherein any C₁-C₆-alkyl moiety is optionally substituted with R³⁸,

20 U is a valence bond, C₁-C₆-alkenylene, -C₁-C₆-alkyl-O- or C₁-C₆-alkylene wherein any C₁-C₆-alkyl moiety is optionally substituted with C₁-C₆-alkyl,

R³⁸ is C₁-C₆-alkyl, aryl, wherein the alkyl or aryl moieties are optionally substituted with one or more substituents independently selected from R³⁹,

25 R³⁹ is independently selected from halogen, cyano, nitro, amino,

M is a valence bond, arylene or heteroarylene, wherein the aryl or heteroaryl moieties are optionally substituted with one or more substituents independently selected from R⁴⁰,

30 R⁴⁰ is selected from

- hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -S(O)₂CF₃, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR⁴¹, -NR⁴¹R⁴², -SR⁴¹, -NR⁴¹S(O)₂R⁴², -S(O)₂NR⁴¹R⁴², -S(O)NR⁴¹R⁴², -S(O)R⁴¹, -S(O)₂R⁴¹, -OS(O)₂R⁴¹,

-C(O)NR⁴¹R⁴², -OC(O)NR⁴¹R⁴², -NR⁴¹C(O)R⁴², -CH₂C(O)NR⁴¹R⁴², -OC₁-C₆-alkyl-C(O)NR⁴¹R⁴², -CH₂OR⁴¹, -CH₂OC(O)R⁴¹, -CH₂NR⁴¹R⁴², -OC(O)R⁴¹, -OC₁-C₆-alkyl-C(O)OR⁴¹, -OC₁-C₆-alkyl-OR⁴¹, -S-C₁-C₆-alkyl-C(O)OR⁴¹, -C₂-C₆-alkenyl-C(=O)OR⁴¹, -NR⁴¹-C(=O)-C₁-C₆-alkyl-C(=O)OR⁴¹, -NR⁴¹-C(=O)-C₁-C₆-alkenyl-C(=O)OR⁴¹, -C(O)OR⁴¹, -C₂-C₆-alkenyl-C(=O)R⁴¹, =O, -NH-C(=O)-O-C₁-C₆-alkyl, or -NH-C(=O)-C(=O)-O-C₁-C₆-alkyl,

5

- C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl, which may each optionally be substituted with one or more substituents selected from R⁴³,

10

• aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, aroyl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-alkenyl or heteroaryl-C₂-C₆-alkynyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R⁴⁴,

15

R⁴¹ and R⁴² are independently selected from hydrogen, -OH, C₁-C₆-alkyl, C₁-C₆-alkenyl, aryl-C₁-C₆-alkyl or aryl, wherein the alkyl moieties may optionally be substituted with one or more substituents independently selected from R⁴⁵, and the aryl moieties may optionally be substituted with one or more substituents independently selected from R⁴⁶; R⁴¹ and R⁴² when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

25

R⁴³ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OR⁴¹, and -NR⁴¹R⁴²

R⁴⁴ is independently selected from halogen, -C(O)OR⁴¹, -CH₂C(O)OR⁴¹, -CH₂OR⁴¹, -CN, -CF₃, -OCF₃, -NO₂, -OR⁴¹, -NR⁴¹R⁴² and C₁-C₆-alkyl,

R⁴⁵ is independently selected from halogen, -CN, -CF₃, -OCF₃, -O-C₁-C₆-alkyl, -C(O)-O-C₁-C₆-alkyl, -COOH and -NH₂,

R⁴⁶ is independently selected from halogen, -C(O)OC₁-C₆-alkyl, -COOH, -CN, -CF₃, -OCF₃, -NO₂, -OH, -OC₁-C₆-alkyl, -NH₂, C(=O) or C₁-C₆-alkyl,

Q is a valence bond, C₁-C₆-alkylene, -C₁-C₆-alkyl-O-, -C₁-C₆-alkyl-NH-, -NH-C₁-C₆-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C₁-C₆-alkyl, -C(=O)-, or -C₁-C₆-alkyl-C(=O)-N(R⁴⁷)- wherein the alkyl moieties are optionally substituted with one or more substituents independently selected from R⁴⁸,

5

R⁴⁷ and R⁴⁸ are independently selected from hydrogen, C₁-C₆-alkyl, aryl optionally substituted with one or more R⁴⁹,

R⁴⁹ is independently selected from halogen and -COOH,

10

T is

- hydrogen,
- C₁-C₆-alkyl, C₂-C₆-alkenyl , C₂-C₆-alkynyl, C₁-C₆-alkyloxy-carbonyl, wherein the alkyl, alkenyl and alkynyl moieties are optionally substituted with one or more substituents independently selected from R⁵⁰,
- aryl, aryloxy, aryloxy-carbonyl, aryl-C₁-C₆-alkyl, aroyl, aryl-C₁-C₆-alkoxy, aryl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkyny-, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-alkenyl, heteroaryl-C₂-C₆-alkynyl,

20

wherein any alkyl, alkenyl , alkynyl, aryl and heteroaryl moiety is optionally substituted with one or more substituents independently selected from R⁵⁰,

R⁵⁰ is C₁-C₆-alkyl, C₁-C₆-alkoxy, aryl, aryloxy, aryl-C₁-C₆-alkoxy, -C(=O)-NH-C₁-C₆-alkyl-aryl, -C(=O)-NR^{50A}-C₁-C₆-alkyl, -C(=O)-NH-(CH₂CH₂O)_mC₁-C₆-alkyl-COOH, heteroaryl, heteroaryl-C₁-C₆-alkoxy, -C₁-C₆-alkyl-COOH, -O-C₁-C₆-alkyl-COOH, -S(O)₂R⁵¹, -C₂-C₆-alkenyl-COOH, -OR⁵¹, -NO₂, halogen, -COOH, -CF₃, -CN, =O, -N(R⁵¹R⁵²), wherein m is 1, 2, 3 or 4, and wherein the aryl or heteroaryl moieties are optionally substituted with one or more R⁵³, and the alkyl moieties are optionally substituted with one or more R^{50B}.

R^{50A} and R^{50B} are independently selected from -C(O)OC₁-C₆-alkyl, -COOH, -C₁-C₆-alkyl-C(O)OC₁-C₆-alkyl, -C₁-C₆-alkyl-COOH, or C₁-C₆-alkyl,

R⁵¹ and R⁵² are independently selected from hydrogen and C₁-C₆-alkyl,

R⁵³ is independently selected from C₁-C₆-alkyl, C₁-C₆-alkoxy, -C₁-C₆-alkyl-COOH, -C₂-C₆-alkenyl-COOH, -OR⁵¹, -NO₂, halogen, -COOH, -CF₃, -CN, or -N(R⁵¹R⁵²),

35

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

In another embodiment hereof K is a valence bond, C₁-C₆-alkylene, -NH-C(=O)-U-, -C₁-C₆-alkyl-S-, -C₁-C₆-alkyl-O-, or -C(=O)-, wherein any C₁-C₆-alkyl moiety is optionally substituted with R³⁸.

In another embodiment hereof K is a valence bond, C₁-C₆-alkylene, -NH-C(=O)-U-, -C₁-C₆-alkyl-S-, or -C₁-C₆-alkyl-O, wherein any C₁-C₆-alkyl moiety is optionally substituted with R³⁸.

In another embodiment hereof K is a valence bond, C₁-C₆-alkylene, or -NH-C(=O)-U, wherein any C₁-C₆-alkyl moiety is optionally substituted with R³⁸.

In another embodiment hereof K is a valence bond or C₁-C₆-alkylene, wherein any C₁-C₆-alkyl moiety is optionally substituted with R³⁸.

In another embodiment hereof K is a valence bond or -NH-C(=O)-U.

In another embodiment hereof K is a valence bond.

15 In another embodiment hereof U is a valence bond or -C₁-C₆-alkyl-O-.

In another embodiment hereof U is a valence bond.

In another embodiment hereof M is arylene or heteroarylene, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R⁴⁰.

20 In another embodiment hereof M is ArG1 or Het1, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R⁴⁰.

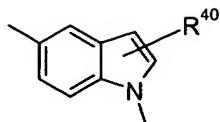
In another embodiment hereof M is ArG1 or Het2, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R⁴⁰.

25 In another embodiment hereof M is ArG1 or Het3, wherein the arylene or heteroarylene moieties are optionally substituted with one or more substituents independently selected from R⁴⁰.

In another embodiment hereof M is phenylene optionally substituted with one or more substituents independently selected from R⁴⁰.

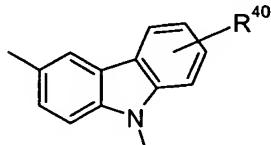
30 In another embodiment hereof M is indolylene optionally substituted with one or more substituents independently selected from R⁴⁰.

In another embodiment hereof M is



In another embodiment hereof M is carbazolylene optionally substituted with one or more substituents independently selected from R⁴⁰.

In another embodiment hereof M is



5

In another embodiment hereof R⁴⁰ is selected from

- hydrogen, halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR⁴¹, -NR⁴¹R⁴², -SR⁴¹, -S(O)₂R⁴¹, -NR⁴¹C(O)R⁴², -OC₁-C₆-alkyl-C(O)NR⁴¹R⁴², -C₂-C₆-alkenyl-C(=O)OR⁴¹, -C(O)OR⁴¹, =O, -NH-C(=O)-O-C₁-C₆-alkyl, or -NH-C(=O)-C(=O)-O-C₁-C₆-alkyl,

10

C₁-C₆-alkyl or C₂-C₆- alkenyl which may each optionally be substituted with one or more substituents independently selected from R⁴³,

15

• aryl, aryloxy, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, or heteroaryl-C₂-C₆-alkenyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R⁴⁴.

In another embodiment hereof R⁴⁰ is selected from

20

- hydrogen, halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR⁴¹, -NR⁴¹R⁴², -SR⁴¹, -S(O)₂R⁴¹, -NR⁴¹C(O)R⁴², -OC₁-C₆-alkyl-C(O)NR⁴¹R⁴², -C₂-C₆-alkenyl-C(=O)OR⁴¹, -C(O)OR⁴¹, =O, -NH-C(=O)-O-C₁-C₆-alkyl, or -NH-C(=O)-C(=O)-O-C₁-C₆-alkyl,

C₁-C₆-alkyl or C₂-C₆- alkenyl which may each optionally be substituted with one or more substituents independently selected from R⁴³,

25

• ArG1, ArG1-O-, ArG1-C₁-C₆-alkoxy, ArG1-C₁-C₆-alkyl, ArG1-C₂-C₆-alkenyl, Het3, Het3-C₁-C₆-alkyl, or Het3-C₂-C₆-alkenyl, wherein the cyclic moieties optionally may be substituted with one or more substituents selected from R⁴⁴.

In another embodiment hereof R⁴⁰ is selected from

30

- hydrogen, halogen, -CF₃, -NO₂, -OR⁴¹, -NR⁴¹R⁴², -C(O)OR⁴¹, =O, or -NR⁴¹C(O)R⁴², • C₁-C₆-alkyl,

- ArG1.

In another embodiment hereof R⁴⁰ is hydrogen.

In another embodiment hereof R⁴⁰ is selected from

- 5
 - Halogen, -NO₂, -OR⁴¹, -NR⁴¹R⁴², -C(O)OR⁴¹, or -NR⁴¹C(O)R⁴²,
 - Methyl,
 - Phenyl.

In another embodiment hereof R⁴¹ and R⁴² are independently selected from hydrogen, C₁-C₆-alkyl, or aryl, wherein the aryl moieties may optionally be substituted with halogen or –COOH.

In another embodiment hereof R⁴¹ and R⁴² are independently selected from hydrogen, methyl, ethyl, or phenyl, wherein the phenyl moieties may optionally be substituted with halogen or –COOH.

In another embodiment hereof Q is a valence bond, C₁-C₆-alkylene, -C₁-C₆-alkyl-O-, -C₁-C₆-alkyl-NH-, -NH-C₁-C₆-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C₁-C₆-alkyl, -C(=O)-, or -C₁-C₆-alkyl-C(=O)-N(R⁴⁷)- wherein the alkyl moieties are optionally substituted with one or more substituents independently selected from R⁴⁸.

In another embodiment hereof Q is a valence bond, -CH₂-, -CH₂-CH₂-, -CH₂-O-, -CH₂-CH₂-O-, -CH₂-NH-, -CH₂-CH₂-NH-, -NH-CH₂-, -NH-CH₂-CH₂-, -NH-C(=O)-, -C(=O)-NH-, -O-CH₂-, 20 -O-CH₂-CH₂-, or -C(=O)-.

In another embodiment hereof R⁴⁷ and R⁴⁸ are independently selected from hydrogen, methyl and phenyl.

In another embodiment hereof T is

- 25
 - Hydrogen,
 - C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R⁵⁰,
 - aryl, aryl-C₁-C₆-alkyl, heteroaryl, wherein the alkyl, aryl and heteroaryl moieties are optionally substituted with one or more substituents independently selected from R⁵⁰.

In another embodiment hereof T is

- 30
 - hydrogen,
 - C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R⁵⁰,
 - ArG1, ArG1-C₁-C₆-alkyl, Het3, wherein the alkyl, aryl and heteroaryl moieties are optionally substituted with one or more substituents independently selected from R⁵⁰.

In another embodiment hereof T is

- hydrogen,
- C₁-C₆-alkyl, optionally substituted with one or more substituents independently selected from R⁵⁰,
- 5 • phenyl, phenyl-C₁-C₆-alkyl, wherein the alkyl and phenyl moieties are optionally substituted with one or more substituents independently selected from R⁵⁰.

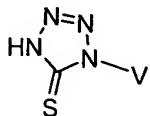
In another embodiment hereof T is phenyl substituted with R⁵⁰.

- 10 In another embodiment hereof R⁵⁰ is C₁-C₆-alkyl, C₁-C₆-alkoxy, aryl, aryloxy, aryl-C₁-C₆-alkoxy, -C(=O)-NH-C₁-C₆-alkyl-aryl, -C(=O)-NR^{50A}-C₁-C₆-alkyl, -C(=O)-NH-(CH₂CH₂O)_mC₁-C₆-alkyl-COOH, heteroaryl, -C₁-C₆-alkyl-COOH, -O-C₁-C₆-alkyl-COOH, -S(O)₂R⁵¹, -C₂-C₆-alkenyl-COOH, -OR⁵¹, -NO₂, halogen, -COOH, -CF₃, -CN, =O, -N(R⁵¹R⁵²), wherein the aryl or heteroaryl moieties are optionally substituted with one or more R⁵³.
- 15 In another embodiment hereof R⁵⁰ is C₁-C₆-alkyl, C₁-C₆-alkoxy, aryl, aryloxy, -C(=O)-NR^{50A}-C₁-C₆-alkyl, -C(=O)-NH-(CH₂CH₂O)_mC₁-C₆-alkyl-COOH, aryl-C₁-C₆-alkoxy, -OR⁵¹, -NO₂, halogen, -COOH, -CF₃, wherein any aryl moiety is optionally substituted with one or more R⁵³.
- 20 In another embodiment hereof R⁵⁰ is C₁-C₆-alkyl, aryloxy, -C(=O)-NR^{50A}-C₁-C₆-alkyl, -C(=O)-NH-(CH₂CH₂O)_mC₁-C₆-alkyl-COOH, aryl-C₁-C₆-alkoxy, -OR⁵¹, halogen, -COOH, -CF₃, wherein any aryl moiety is optionally substituted with one or more R⁵³.
- 25 In another embodiment hereof R⁵⁰ is C₁-C₆-alkyl, ArG1-O-, -C(=O)-NR^{50A}-C₁-C₆-alkyl, -C(=O)-NH-(CH₂CH₂O)_mC₁-C₆-alkyl-COOH, ArG1-C₁-C₆-alkoxy, -OR⁵¹, halogen, -COOH, -CF₃, wherein any aryl moiety is optionally substituted with one or more R⁵³.
- In another embodiment hereof R⁵⁰ is -C(=O)-NR^{50A}CH₂, -C(=O)-NH-(CH₂CH₂O)₂CH₂I-COOH, or -C(=O)-NR^{50A}CH₂CH₂.
- In another embodiment hereof R⁵⁰ is phenyl, methyl or ethyl.
- In another embodiment hereof R⁵⁰ is methyl or ethyl.
- In another embodiment hereof m is 1 or 2.
- In another embodiment hereof R⁵¹ is methyl.
- 30 In another embodiment hereof R⁵³ is C₁-C₆-alkyl, C₁-C₆-alkoxy, -OR⁵¹, halogen, or -CF₃.
- In another embodiment hereof R^{50A} is -C(O)OCH₃, -C(O)OCH₂CH₃ -COOH, -CH₂C(O)OCH₃, -CH₂C(O)OCH₂CH₃, -CH₂CH₂C(O)OCH₃, -CH₂CH₂C(O)OCH₂CH₃, -CH₂COOH, methyl, or ethyl.

In another embodiment hereof R^{50B} is $-C(O)OCH_3$, $-C(O)OCH_2CH_3$, $-COOH$, $-CH_2C(O)OCH_3$, $-CH_2C(O)OCH_2CH_3$, $-CH_2CH_2C(O)OCH_3$, $-CH_2CH_2C(O)OCH_2CH_3$, $-CH_2COOH$, methyl, or ethyl.

In another embodiment hereof the zinc-binding ligand is

5



wherein V is C_1-C_6 -alkyl, aryl, heteroaryl, aryl- C_{1-6} -alkyl- or aryl- C_{2-6} -alkenyl-, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R^{54} , and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R^{55} ,

R^{54} is independently selected from halogen, $-CN$, $-CF_3$, $-OCF_3$, aryl, $-COOH$ and $-NH_2$,

R^{55} is independently selected from

15 •hydrogen, halogen, $-CN$, $-CH_2CN$, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2CF_3$,
 $-OCF_2CHF_2$, $-S(O)_2CF_3$, $-OS(O)_2CF_3$, $-SCF_3$, $-NO_2$, $-OR^{56}$, $-NR^{56}R^{57}$, $-SR^{56}$,
 $-NR^{56}S(O)_2R^{57}$, $-S(O)_2NR^{56}R^{57}$, $-S(O)NR^{56}R^{57}$, $-S(O)R^{56}$, $-S(O)_2R^{56}$, $-OS(O)_2R^{56}$,
 $-C(O)NR^{56}R^{57}$, $-OC(O)NR^{56}R^{57}$, $-NR^{56}C(O)R^{57}$, $-CH_2C(O)NR^{56}R^{57}$, $-OC_1-C_6$ -
alkyl- $C(O)NR^{56}R^{57}$, $-CH_2OR^{56}$, $-CH_2OC(O)R^{56}$, $-CH_2NR^{56}R^{57}$, $-OC(O)R^{56}$, $-OC_1-C_8$ -
20 alkyl- $C(O)OR^{56}$, $-OC_1-C_8$ -alkyl- OR^{56} , $-SC_1-C_6$ -alkyl- $C(O)OR^{56}$, $-C_2-C_6$ -alkenyl-
 $C(=O)OR^{56}$, $-NR^{56}-C(=O)-C_1-C_6$ -alkyl- $C(=O)OR^{56}$, $-NR^{56}-C(=O)-C_1-C_6$ -
alkenyl- $C(=O)OR^{56}$, $-C(O)OR^{56}$, or $-C_2-C_6$ -alkenyl- $C(=O)R^{56}$,

• C_1-C_6 -alkyl, C_2-C_6 -alkenyl or C_2-C_6 -alkynyl,

25

which may optionally be substituted with one or more substituents selected from R^{58} ,

30 •aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl- C_1-C_6 -alkoxy, aryl- C_1-C_6 -alkyl,
aryl- C_2-C_6 -alkenyl, aroyl- C_2-C_6 -alkenyl, aryl- C_2-C_6 -alkynyl, heteroaryl, heteroaryl- C_1-C_6 -alkyl, heteroaryl- C_2-C_6 -alkenyl or heteroaryl- C_2-C_6 -alkynyl,

of which the cyclic moieties optionally may be substituted with one or more substituents selected from R^{59} ,

- R⁵⁶ and R⁵⁷ are independently selected from hydrogen, OH, CF₃, C₁-C₁₂-alkyl, aryl-C₁-C₆-alkyl, -C(=O)-C₁-C₆-alkyl or aryl, wherein the alkyl groups may optionally be substituted with one or more substituents independently selected from R⁶⁰, and the aryl groups may 5 optionally be substituted with one or more substituents independently selected from R⁶¹; R⁵⁶ and R⁵⁷ when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,
- 10 R⁵⁸ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OR⁵⁶, and -NR⁵⁶R⁵⁷,
- R⁵⁹ is independently selected from halogen, -C(O)OR⁵⁶, -CH₂C(O)OR⁵⁶, -CH₂OR⁵⁶, -CN, -CF₃, -OCF₃, -NO₂, -OR⁵⁶, -NR⁵⁶R⁵⁷ and C₁-C₆-alkyl,
- 15 R⁶⁰ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OC₁-C₆-alkyl, -C(O)OC₁-C₆-alkyl, -C(=O)-R⁶², -COOH and -NH₂,
- R⁶¹ is independently selected from halogen, -C(O)OC₁-C₆-alkyl, -COOH, -CN, -CF₃, -OCF₃, -NO₂, -OH, -OC₁-C₆-alkyl, -NH₂, C(=O) or C₁-C₆-alkyl,
- 20 R⁶² is C₁-C₆-alkyl, aryl optionally substituted with one or more substituents independently selected from halogen, or heteroaryl optionally substituted with one or more C₁-C₆-alkyl independently,
- 25 or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

In another embodiment hereof V is aryl, heteroaryl, or aryl-C₁-C₆-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected R⁵⁴, and the aryl 30 or heteroaryl is optionally substituted with one or more substituents independently selected from R⁵⁵.

In another embodiment hereof V is aryl, Het1, or aryl-C₁-C₆-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R⁵⁴, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently 35 selected from R⁵⁵.

In another embodiment hereof V is aryl, Het2, or aryl-C₁₋₆-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R⁵⁴, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R⁵⁵.

- 5 In another embodiment hereof V is aryl, Het3, or aryl-C₁₋₆-alkyl-, wherein the alkyl is optionally substituted with one or more substituents independently selected from R⁵⁴, and the aryl or heteroaryl moiety is optionally substituted with one or more substituents independently selected from R⁵⁵.

10 In another embodiment hereof V is aryl optionally substituted with one or more substituents independently selected from R⁵⁵.

In another embodiment hereof V is ArG1 optionally substituted with one or more substituents independently selected from R⁵⁵.

In another embodiment hereof V is phenyl, naphthyl or anthranyl optionally substituted with one or more substituents independently selected from R⁵⁵.

- 15 In another embodiment hereof V is phenyl optionally substituted with one or more substituents independently selected from R⁵⁵.

In another embodiment hereof R⁵⁵ is independently selected from

- halogen, C₁-C₆-alkyl, -CN, -OCF₃, -CF₃, -NO₂, -OR⁵⁶, -NR⁵⁶R⁵⁷, -NR⁵⁶C(O)R⁵⁷ -SR⁵⁶, -OC₁-C₈-alkyl-C(O)OR⁵⁶, or -C(O)OR⁵⁶,

- 20 • C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R⁵⁸

- aryl, aryl-C₁-C₆-alkyl, heteroaryl, or heteroaryl-C₁-C₆-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents independently selected from R⁵⁹.

- 25 In another embodiment hereof R⁵⁵ is independently selected from

- halogen, C₁-C₆-alkyl, -CN, -OCF₃, -CF₃, -NO₂, -OR⁵⁶, -NR⁵⁶R⁵⁷, -NR⁵⁶C(O)R⁵⁷ -SR⁵⁶, -OC₁-C₈-alkyl-C(O)OR⁵⁶, or -C(O)OR⁵⁶

- C₁-C₆-alkyl optionally substituted with one or more substituents independently selected from R⁵⁸

- 30 • ArG1, ArG1-C₁-C₆-alkyl, Het3, or Het3-C₁-C₆-alkyl

of which the cyclic moieties optionally may be substituted with one or more substituents independently selected from R⁵⁹.

In another embodiment hereof R⁵⁵ is independently selected from halogen, -OR⁵⁶, -NR⁵⁶R⁵⁷,

- 35 -C(O)OR⁵⁶, -OC₁-C₈-alkyl-C(O)OR⁵⁶, -NR⁵⁶C(O)R⁵⁷ or C₁-C₆-alkyl.

In another embodiment hereof R⁵⁵ is independently selected from halogen, -OR⁵⁶, -NR⁵⁶R⁵⁷, -C(O)OR⁵⁶, -OC₁-C₈-alkyl-C(O)OR⁵⁶, -NR⁵⁶C(O)R⁵⁷, methyl or ethyl.

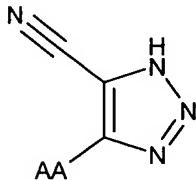
In another embodiment hereof R⁵⁶ and R⁵⁷ are independently selected from hydrogen, CF₃, C₁-C₁₂-alkyl, or -C(=O)-C₁-C₆-alkyl; R⁵⁶ and R⁵⁷ when attached to the same nitrogen atom

5 may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

In another embodiment hereof R⁵⁶ and R⁵⁷ are independently selected from hydrogen or C₁-C₁₂-alkyl, R⁵⁶ and R⁵⁷ when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

In another embodiment hereof R⁵⁶ and R⁵⁷ are independently selected from hydrogen or 10 methyl, ethyl, propyl butyl, R⁵⁶ and R⁵⁷ when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom.

In another embodiment hereof the zinc-binding ligand is



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wherein AA is C₁-C₆-alkyl, aryl, heteroaryl, aryl-C₁₋₆-alkyl- or aryl-C₂₋₆-alkenyl-, wherein the alkyl or alkenyl is optionally substituted with one or more substituents independently selected from R⁶³, and the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from R⁶⁴,

20

R⁶³ is independently selected from halogen, -CN, -CF₃, -OCF₃, aryl, -COOH and -NH₂,

R⁶⁴ is independently selected from

25

- hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -S(O)₂CF₃, -OS(O)₂CF₃, -SCF₃, -NO₂, -OR⁶⁵, -NR⁶⁵R⁶⁶, -SR⁶⁵, -NR⁶⁵S(O)₂R⁶⁶, -S(O)₂NR⁶⁵R⁶⁶, -S(O)NR⁶⁵R⁶⁶, -S(O)R⁶⁵, -S(O)₂R⁶⁵, -OS(O)₂R⁶⁵, -C(O)NR⁶⁵R⁶⁶, -OC(O)NR⁶⁵R⁶⁶, -NR⁶⁵C(O)R⁶⁶, -CH₂C(O)NR⁶⁵R⁶⁶, -OC₁-C₆-alkyl-C(O)NR⁶⁵R⁶⁶, -CH₂OR⁶⁵, -CH₂OC(O)R⁶⁵, -CH₂NR⁶⁵R⁶⁶, -OC(O)R⁶⁵, -OC₁-C₆-alkyl-C(O)OR⁶⁵, -OC₁-C₆-alkyl-OR⁶⁵, -SC₁-C₆-alkyl-C(O)OR⁶⁵, -C₂-C₆-alkenyl-C(=O)OR⁶⁵, -NR⁶⁵-C(=O)-C₁-C₆-alkyl-C(=O)OR⁶⁵, -NR⁶⁵-C(=O)-C₁-C₆-alkenyl-C(=O)OR⁶⁵, -C(O)OR⁶⁵, or -C₂-C₆-alkenyl-C(=O)R⁶⁵,

30

•C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl, each of which may optionally be substituted with one or more substituents selected from R⁶⁷,

5 •aryl, aryloxy, aryloxycarbonyl, aroyl, arylsulfanyl, aryl-C₁-C₆-alkoxy, aryl-C₁-C₆-alkyl, aryl-C₂-C₆-alkenyl, aroyl-C₂-C₆-alkenyl, aryl-C₂-C₆-alkynyl, heteroaryl, heteroaryl-C₁-C₆-alkyl, heteroaryl-C₂-C₆-alkenyl or heteroaryl-C₂-C₆-alkynyl,

10 of which the cyclic moieties optionally may be substituted with one or more substituents selected from R⁶⁸,

R⁶⁵ and R⁶⁶ are independently selected from hydrogen, OH, CF₃, C₁-C₁₂-alkyl, aryl-C₁-C₆-alkyl, -C(=O)-R⁶⁹, aryl or heteroaryl, wherein the alkyl groups may optionally be substituted with one or more substituents selected from R⁷⁰, and the aryl and heteroaryl groups may 15 optionally be substituted with one or more substituents independently selected from R⁷¹; R⁶⁵ and R⁶⁶ when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds,

20

R⁶⁷ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OR⁶⁵, and -NR⁶⁵R⁶⁶,

R⁶⁸ is independently selected from halogen, -C(O)OR⁶⁵, -CH₂C(O)OR⁶⁵, -CH₂OR⁶⁵, -CN, -CF₃, -OCF₃, -NO₂, -OR⁶⁵, -NR⁶⁵R⁶⁶ and C₁-C₆-alkyl,

25

R⁶⁹ is independently selected from C₁-C₆-alkyl, aryl optionally substituted with one or more halogen, or heteroaryl optionally substituted with one or more C₁-C₆-alkyl,

R⁷⁰ is independently selected from halogen, -CN, -CF₃, -OCF₃, -OC₁-C₆-alkyl, -C(O)OC₁-C₆-alkyl, -COOH and -NH₂,

R⁷¹ is independently selected from halogen, -C(O)OC₁-C₆-alkyl, -COOH, -CN, -CF₃, -OCF₃, -NO₂, -OH, -OC₁-C₆-alkyl, -NH₂, C(=O) or C₁-C₆-alkyl,

or any enantiomer, diastereomer, including a racemic mixture, tautomer as well as a salt thereof with a pharmaceutically acceptable acid or base.

In another embodiment hereof AA is aryl, heteroaryl or aryl-C₁₋₆-alkyl-, wherein the alkyl is optionally substituted with one or more R⁶³, and the aryl or heteroaryl is optionally substituted

5 with one or more substituents independently selected from R⁶⁴.

In another embodiment hereof AA is aryl or heteroaryl optionally substituted with one or more substituents independently selected from R⁶⁴.

In another embodiment hereof AA is ArG1 or Het1 optionally substituted with one or more substituents independently selected from R⁶⁴.

10 In another embodiment hereof AA is ArG1 or Het2 optionally substituted with one or more substituents independently selected from R⁶⁴.

In another embodiment hereof AA is ArG1 or Het3 optionally substituted with one or more substituents independently selected from R⁶⁴.

15 In another embodiment hereof AA is phenyl, naphtyl, anthryl, carbazolyl, thienyl, pyridyl, or benzodioxyl optionally substituted with one or more substituents independently selected from R⁶⁴.

In another embodiment hereof AA is phenyl or naphtyl optionally substituted with one or more substituents independently selected from R⁶⁴.

20 In another embodiment hereof R⁶⁴ is independently selected from hydrogen, halogen, -CF₃, -OCF₃, -OR⁶⁵, -NR⁶⁵R⁶⁶, C₁-C₆-alkyl, -OC(O)R⁶⁵, -OC₁-C₆-alkyl-C(O)OR⁶⁵, aryl-C₂-C₆-alkenyl, aryloxy or aryl, wherein C₁-C₆-alkyl is optionally substituted with one or more substituents independently selected from R⁶⁷, and the cyclic moieties optionally are substituted with one or more substituents independently selected from R⁶⁸.

25 In another embodiment hereof R⁶⁴ is independently selected from halogen, -CF₃, -OCF₃, -OR⁶⁵, -NR⁶⁵R⁶⁶, methyl, ethyl, propyl, -OC(O)R⁶⁵, -OCH₂-C(O)OR⁶⁵, -OCH₂-CH₂-C(O)OR⁶⁵, phenoxy optionally substituted with one or more substituents independently selected from R⁶⁸.

30 In another embodiment hereof R⁶⁵ and R⁶⁶ are independently selected from hydrogen, CF₃, C₁-C₁₂-alkyl, aryl, or heteroaryl optionally substituted with one or more substituents independently selected from R⁷¹.

In another embodiment hereof R⁶⁵ and R⁶⁶ are independently hydrogen, C₁-C₁₂-alkyl, aryl, or heteroaryl optionally substituted with one or more substituents independently selected from R⁷¹.

In another embodiment hereof R⁶⁵ and R⁶⁶ are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het1 optionally substituted with one or more substituents independently selected from R⁷¹.

5 In another embodiment hereof R⁶⁵ and R⁶⁶ are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het2 optionally substituted with one or more substituents independently selected from R⁷¹.

In another embodiment hereof R⁶⁵ and R⁶⁶ are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, ArG1 or Het3 optionally substituted with one or more substituents independently selected from R⁷¹.

10 In another embodiment hereof R⁶⁵ and R⁶⁶ are independently hydrogen, methyl, ethyl, propyl, butyl, 2,2-dimethyl-propyl, phenyl, naphtyl, thiadiazolyl optionally substituted with one or more R⁷¹ independently; or isoxazolyl optionally substituted with one or more substituents independently selected from R⁷¹.

In another embodiment hereof R⁷¹ is halogen or C₁-C₆-alkyl.

15 In another embodiment hereof R⁷¹ is halogen or methyl.

The following aspects are also provided by the present invention, wherein the compounds of the invention may be any of the above described embodiments.

20 In one aspect the invention provides a pharmaceutical composition wherein the insulin is rapid acting insulin.

In another embodiment the invention provides a pharmaceutical composition wherein the insulin is selected from the group consisting of human insulin, an analogue thereof, a derivative thereof, and combinations of any of these.

25 In another embodiment the invention provides a pharmaceutical composition wherein the insulin is an analogue of human insulin selected from the group consisting of

i.An analogue wherein position B28 is Asp, Lys, Leu, Val, or Ala and position B29 is Lys or Pro; and

ii.des(B28-B30), des(B27) or des(B30) human insulin.

30

In another embodiment the invention provides a pharmaceutical composition wherein the insulin is an analogue of human insulin wherein position B28 is Asp or Lys, and position B29 is Lys or Pro.

35 In another embodiment the invention provides a pharmaceutical composition wherein the insulin is des(B30) human insulin.

In another embodiment the invention provides a pharmaceutical composition wherein the insulin is an analogue of human insulin wherein position B3 is Lys and position B29 is Glu or Asp.

5 In another embodiment the invention provides a pharmaceutical composition wherein the insulin is a derivative of human insulin having one or more lipophilic substituents.

In another embodiment the invention provides a pharmaceutical composition wherein the insulin derivative is selected from the group consisting of B29-N^ε-myristoyl-des(B30) human insulin, B29-N^ε-palmitoyl-des(B30) human insulin, B29-N^ε-myristoyl human insulin, B29-N^ε-palmitoyl human insulin, B28-N^ε-myristoyl Lys^{B28} Pro^{B29} human insulin, B28-N^ε-palmitoyl 10 Lys^{B28} Pro^{B29} human insulin, B30-N^ε-myristoyl-Thr^{B29}Lys^{B30} human insulin, B30-N^ε-palmitoyl-Thr^{B29}Lys^{B30} human insulin, B29-N^ε-(N-palmitoyl-γ-glutamyl)-des(B30) human insulin, B29-N^ε-(N-lithocholy-γ-glutamyl)-des(B30) human insulin, B29-N^ε-(ω-carboxyheptadecanoyl)-des(B30) human insulin and B29-N^ε-(ω-carboxyheptadecanoyl) human insulin.

15 In another embodiment the invention provides a pharmaceutical composition wherein the insulin derivative is B29-N^ε-myristoyl-des(B30) human insulin.

In another embodiment the invention provides a pharmaceutical composition comprising 2-6 moles zinc²⁺ ions per mole insulin.

In another embodiment the invention provides a pharmaceutical composition comprising 2-3 moles zinc²⁺ ions per mole insulin.

20 In another embodiment the invention provides a pharmaceutical composition further comprising at least 3 molecules of a phenolic compound per insulin hexamer.

In another embodiment the invention provides a pharmaceutical composition further comprising an isotonicity agent.

25 In another embodiment the invention provides a pharmaceutical composition further comprising a buffer substance.

A method of stabilising an insulin composition comprising adding a zinc-binding ligand to the insulin composition.

30 A method of treating type 1 or type 2 diabetes comprising administering to a patient in need thereof a pharmaceutically effective dose of an insulin composition.

In one embodiment of the invention the concentration of added ligand for the zinc site is between 0.2 and 10 times that of zinc ion in the preparation. In another embodiment the

concentration is between 0.5 and 5 times that of zinc ion. In another embodiment the ligand concentration is identical to that of zinc ion in the preparation.

The compounds of the present invention may be chiral, and it is intended that any 5 enantiomers, as separated, pure or partially purified enantiomers or racemic mixtures thereof are included within the scope of the invention.

Furthermore, when a double bond or a fully or partially saturated ring system or more than one centre of asymmetry or a bond with restricted rotatability is present in the molecule 10 diastereomers may be formed. It is intended that any diastereomers, as separated, pure or partially purified diastereomers or mixtures thereof are included within the scope of the invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms, which the compounds are able to form, are included within the scope of the present invention.

15 The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulphuric, 20 nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, picric, pyruvic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, , ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids 25 and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, 30 n-butyl-, sec-butyl-, tert-butyl-, tetramethylammonium salts and the like.

Also intended as pharmaceutically acceptable acid addition salts are the hydrates, which the present compounds, are able to form.

Furthermore, the pharmaceutically acceptable salts comprise basic amino acid salts such as lysine, arginine and ornithine.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

- 5 The compounds of the present invention may form solvates with standard low molecular weight solvents using methods well known to the person skilled in the art. Such solvates are also contemplated as being within the scope of the present invention.

In one embodiment of the invention the stabilized preparations are used in connection with insulin pumps. The insulin pumps may be prefilled and disposable, or the insulin compositions may be supplied from a reservoir which is removable. Insulin pumps may be skin-mounted or carried, and the path of the insulin composition from the storage compartment of the pump to the patient may be more or less tortuous. The elevated temperature and increased physical stress the insulin composition is thus exposed to challenges the stability of the constituent insulin. Non-limiting examples of insulin pumps are disclosed in US 5,957,895, US 5,858,001, US 4,468,221, US 4,468,221, US 5,957,895, US 5,858,001, US 6,074,369, US 5,858,001, US 5,527,288, and US 6,074,369.

In another embodiment the stabilized preparations are used in connection with pen-like injection devices, which may be prefilled and disposable, or the insulin compositions may be supplied from a reservoir which is removable. Non-limiting examples of pen-like injection devices are FlexPen®, InnoLet®, InDuo™, Innovo®.

In a further embodiment stabilized preparations are used in connection with devices for pulmonary administration of aqueous insulin compositions, a non-limiting example of which is the AerX® device.

In one aspect of the invention, the ligands are added to rapid acting insulin. The resulting preparations have improved physical and chemical stability while still retaining a high rate of absorption from subcutaneous tissue.

The present invention also relates to pharmaceutical compositions for the treatment of diabetes in a patient in need of such a treatment comprising an R-state hexamer of insulin according to the invention together with a pharmaceutically acceptable carrier.

In one embodiment of the invention the insulin composition comprises 60 to 3000 nmol/ml of insulin.

In another embodiment of the invention the insulin composition comprises 240 to 1200 nmol/ml of insulin.

- 5 In another embodiment of the invention the insulin composition comprises about 600 nmol/ml of insulin.

Zinc ions may be present in an amount corresponding to 13 to 33 µg Zn/100 U insulin, more preferably 15 to 26 µg Zn/100 U insulin.

- 10 Insulin formulations of the invention are usually administered from multi-dose containers where a preservative effect is desired. Since phenolic preservatives also stabilize the R-state hexamer the formulations may contain up to 50 mM of phenolic molecules. Non-limiting examples of phenolic molecules are phenol, m-cresol, chloro-cresol, thymol, 7-hydroxyindole or any mixture thereof.

In one embodiment of the invention 0.5 to 4.0 mg/ml of phenolic compound may be employed.

- 15 In another embodiment of the invention 0.6 to 4.0 mg/ml of m-cresol may be employed.

In another embodiment of the invention 0.5 to 4.0 mg/ml of phenol may be employed.

In another embodiment of the invention 1.4 to 4.0 mg/ml of phenol may be employed.

In another embodiment of the invention 0.5 to 4.0 mg/ml of a mixture of m-cresol or phenol may be employed.

- 20 In another embodiment of the invention 1.4 to 4.0 mg/ml of a mixture of m-cresol or phenol may be employed.

The pharmaceutical composition may further comprise a buffer substance, such as a TRIS, phosphate, glycine or glycylglycine (or another zwitterionic substance) buffer, an isotonicity agent, such as NaCl, glycerol, mannitol and/or lactose. Chloride would be used at moderate concentrations, in one embodiment of the invention up to 50 mM to avoid competition with the zinc-site ligands of the present invention. In another embodiment the chloride concentration would be from 3 to 20 mM.

The *in vivo* action of insulin may be modified by the addition of physiologically acceptable agents that increase the viscosity of the pharmaceutical composition. Thus, the

- 30 pharmaceutical composition according to the invention may furthermore comprise an agent which increases the viscosity, such as polyethylene glycol, polypropylene glycol, copolymers thereof, dextrans and/or polylactides.

In one embodiment the insulin composition of the invention comprises between 0.0005 % by weight and 1 % by weight of a non-ionic or zwitter-ionic surfactant, for example tween 20 or

Polox 188. A nonionic detergent can be added to stabilise insulin against fibrillation during storage and handling.

The insulin composition of the present invention may have a pH value in the range of 3.0 to 8.5, e.g. 7.4 to 7.9.

5

EXAMPLES

The following examples and general procedures refer to intermediate compounds and final products identified in the specification and in the synthesis schemes. The preparation of the compounds of the present invention is described in detail using the following examples, but the chemical reactions described are disclosed in terms of their general applicability to the preparation of compounds of the invention. Occasionally, the reaction may not be applicable as described to each compound included within the disclosed scope of the invention. The compounds for which this occurs will be readily recognised by those skilled in the art. In these cases the reactions can be successfully performed by conventional modifications known to those skilled in the art, that is, by appropriate protection of interfering groups, by changing to other conventional reagents, or by routine modification of reaction conditions. Alternatively, other reactions disclosed herein or otherwise conventional will be applicable to the preparation of the corresponding compounds of the invention. In all preparative methods, all starting materials are known or may easily be prepared from known starting materials. All temperatures are set forth in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight when referring to yields and all parts are by volume when referring to solvents and eluents.

25

HPLC-MS (Method A)

The following instrumentation was used:

- Hewlett Packard series 1100 G1312A Bin Pump
- Hewlett Packard series 1100 Column compartment
- 30 • Hewlett Packard series 1100 G13 15A DAD diode array detector
- Hewlett Packard series 1100 MSD

The instrument was controlled by HP Chemstation software.

The HPLC pump was connected to two eluent reservoirs containing:

- A: 0.01% TFA in water
- B: 0.01% TFA in acetonitrile

The analysis was performed at 40 °C by injecting an appropriate volume of the sample

- 5 (preferably 1 µL) onto the column, which was eluted with a gradient of acetonitrile.

The HPLC conditions, detector settings and mass spectrometer settings used are given in the following table.

Column	Waters Xterra MS C-18 X 3 mm id
Gradient	10% - 100% acetonitrile lineary during 7.5 min at 1.0 mL/min
Detection	UV: 210 nm (analog output from DAD)
MS	Ionisation mode: API-ES Scan 100-1000 amu step 0.1 amu

10 **HPLC-MS (Method B)**

The following instrumentation was used:

Sciex API 100 Single quadropole mass spectrometer

Perkin Elmer Series 200 Quard pump

Perkin Elmer Series 200 autosampler

15 Applied Biosystems 785A UV detector

Sedex 55 evaporative light scattering detector

A Valco column switch with a Valco actuator controlled by timed events from the pump.

The Sciex Sample control software running on a Macintosh PowerPC 7200 computer was

- 20 used for the instrument control and data acquisition.

The HPLC pump was connected to four eluent reservoirs containing:

- A: Acetonitrile
- B: Water
- C: 0.5% TFA in water
- D: 0.02 M ammonium acetate

The requirements for samples are that they contain approximately 500 µg/mL of the compound to be analysed in an acceptable solvent such as methanol, ethanol, acetonitrile, THF, water and mixtures thereof. (High concentrations of strongly eluting solvents will interfere with the chromatography at low acetonitrile concentrations.)

5

The analysis was performed at room temperature by injecting 20 µL of the sample solution on the column, which was eluted with a gradient of acetonitrile in either 0.05% TFA or 0.002 M ammonium acetate. Depending on the analysis method varying elution conditions were used.

10

The eluate from the column was passed through a flow splitting T-connector, which passed approximately 20 µL/min through approx. 1 m. 75 µ fused silica capillary to the API interface of API 100 spectrometer.

15 The remaining 1.48 mL/min was passed through the UV detector and to the ELS detector.

During the LC-analysis the detection data were acquired concurrently from the mass spectrometer, the UV detector and the ELS detector.

20 The LC conditions, detector settings and mass spectrometer settings used for the different methods are given in the following table.

Column	YMC ODS-A 120Å s - 5µ 3 mm x 50 mm id	
Gradient	5% - 90% acetonitrile in 0.05% TFA linearly during 7.5 min at 1.5 mL/min	
Detection	UV: 214 nm	ELS: 40 °C
MS	Experiment: Start: 100 amu Stop: 800 amu Step: 0.2 amu Dwell: 0.571 msec Method: Scan 284 times = 9.5 min	

HPLC-MS (Method C) The following instrumentation is used:

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- Hewlett Packard series 1100 G1312A Bin Pump
- Hewlett Packard series 1100 Column compartment
- Hewlett Packard series 1100 G1315A DAD diode array detector

90

- Hewlett Packard series 1100 MSD
- Sedex 55 Evaporative Light Scattering detector

The instrument is controlled by HP Chemstation software.

The HPLC pump is connected to two eluent reservoirs containing:

A	0.01% TFA in water
B	0.01% TFA in acetonitrile

5

The analysis is performed at 40 °C by injecting an appropriate volume of the sample (preferably 1 µl) onto the column which is eluted with a gradient of acetonitrile.

The HPLC conditions, detector settings and mass spectrometer settings used are given in the following table.

Column	Waters Xterra MS C-18 X 3 mm id 5 µm
Gradient	5% - 100% acetonitrile linear during 7.5 min at 1.5 ml/min
Detection	210 nm (analogue output from DAD) ELS (analogue output from ELS)
MS	ionisation mode API-ES Scan 100-1000 amu step 0.1 amu

10

After the DAD the flow is divided yielding approximately 1 ml/min to the ELS and 0.5 ml/min to the MS.

HPLC-MS (Method D)

15 The following instrumentation was used:

Sciex API 150 Single Quadropole mass spectrometer

Hewlett Packard Series 1100 G1312A Bin pump

Gilson 215 micro injector

Hewlett Packard Series 1100 G1315A DAD diode array detector

20 Sedex 55 evaporative light scattering detector

A Valco column switch with a Valco actuator controlled by timed events from the pump.

The Sciex Sample control software running on a Macintosh Power G3 computer was used for the instrument control and data acquisition.

The HPLC pump was connected to two eluent reservoirs containing:

- A: Acetonitrile containing 0.05% TFA
- B: Water containing 0.05% TFA

The requirements for the samples are that they contain approximately 500 µg/ml of the compound to be analysed in an acceptable solvent such as methanol, ethanol, acetonitrile, THF, water and mixtures thereof. (High concentrations of strongly eluting solvents will

- 5 interfere with the chromatography at low acetonitrile concentrations.)

The analysis was performed at room temperature by injecting 20 µl of the sample solution on the column, which was eluted with a gradient of acetonitrile in 0.05% TFA

The eluate from the column was passed through a flow splitting T-connector, which passed approximately 20 µl/min through approx. 1 m 75 µ fused silica capillary to the API interface of

- 10 API 150 spectrometer.

The remaining 1.48 ml/min was passed through the UV detector and to the ELS detector.

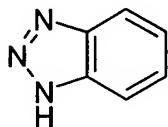
During the LC-analysis the detection data were acquired concurrently from the mass spectrometer, the UV detector and the ELS detector.

- 15 The LC conditions, detector settings and mass spectrometer settings used for the different methods are given in the following table.

Column	Waters X-terra C18 5µ 3 mm x 50 mm id		
Gradient	5% - 90% acetonitrile in 0.05% TFA linearly during 7.5 min at 1.5 ml/min		
Detection	UV: 214 nm		ELS: 40 °C
MS	Experiment:	Start: 100 amu	Stop: 800 amu
	Dwell:	0.571 msec	Step: 0.2 amu
	Method:	Scan 284 times = 9.5 min	

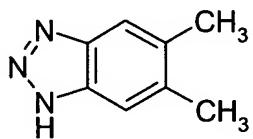
EXAMPLES

0102-0000-0273 Example 1 HBOL

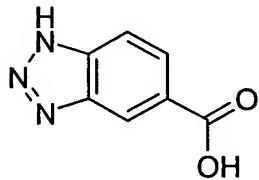
1*H*-Benzotriazole

5

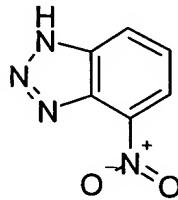
0102-0000-0274 Example 2 HBOL

5,6-Dimethyl-1*H*-benzotriazole

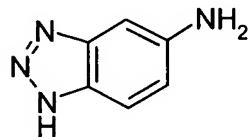
10 0102-0000-0275 Example 3 HBOL

1*H*-Benzotriazole-5-carboxylic acid

0102-0000-0280 Example 4 HBOL

15 4-Nitro-1*H*-benzotriazole

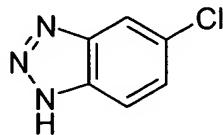
0102-0000-0284 Example 5 HBOL

5-Amino-1*H*-benzotriazole

20

0102-0000-0287 Example 6 HBOL

5-Chloro-1*H*-benzotriazole



5

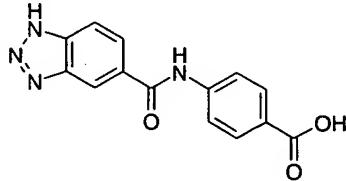
0102-0000-0286 Example 7 HBOL

5-Nitro-1*H*-benzotriazole



0102-0000-3015 Example 8 PEM

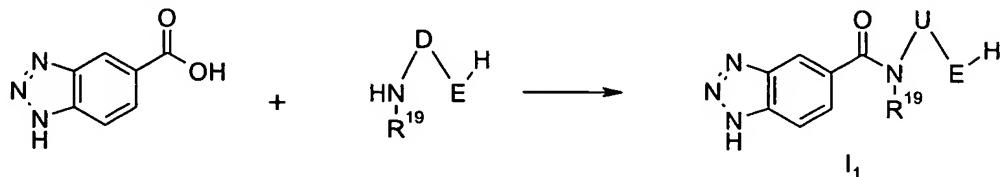
10 4-[(1*H*-Benzotriazole-5-carbonyl)amino]benzoic acid



4-[(1*H*-Benzotriazole-5-carbonyl)amino]benzoic acid methyl ester (5.2 g, 17.6 mmol) was dissolved in THF (60 mL) and methanol (10 mL) was added followed by 1N sodium hydroxide (35 mL). The mixture was stirred at room temperature for 16 hours and then 1N hydrochloric acid (45 mL) was added. The mixture was added water (200 mL) and extracted with ethyl acetate (2 x 500 mL). The combined organic phases were evaporated *in vacuo* to afford 0.44 g of 4-[(1*H*-benzotriazole-5-carbonyl)amino]benzoic acid. By filtration of the aqueous phase a further crop of 4-[(1*H*-benzotriazole-5-carbonyl)amino]benzoic acid was isolated (0.52 g).

20

¹H-NMR (DMSO-d₆): δ 7.97 (4H, s), 8.03 (2H, m), 8.66 (1H, bs), 10.7 (1H, s), 12.6 (1H, bs); HPLC-MS (Method A): m/z: 283 (M+1); Rt = 1.85 min.

General procedure (A) for preparation of compounds of general formula I₁:

wherein D, E and R¹⁹ are as defined above, and E is optionally substituted with up to three substituents R²¹, R²² and R²³ independently as defined above.

5

The carboxylic acid of 1H-benzotriazole-5-carboxylic acid is activated, ie the OH functionality is converted into a leaving group L (selected from eg fluorine, chlorine, bromine, iodine, 1-imidazolyl, 1,2,4-triazolyl, 1-benzotriazolyloxy, 1-(4-aza benzotriazolyl)oxy, pentafluorophenoxy, N-succinyloxy 3,4-dihydro-4-oxo-3-(1,2,3-benzotriazinyl)oxy,

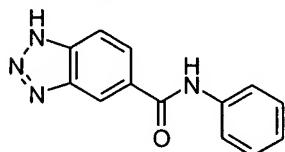
- 10 benzotriazole 5-COO, or any other leaving group known to act as a leaving group in acylation reactions. The activated benzotriazole-5-carboxylic acid is then reacted with R²-(CH₂)_n-B' in the presence of a base. The base can be either absent (i.e. R²-(CH₂)_n-B' acts as a base) or triethylamine, N-ethyl-N,N.-diisopropylamine, N-methylmorpholine, 2,6-lutidine, 2,2,6,6-tetramethylpiperidine, potassium carbonate, sodium carbonate, caesium carbonate or any
- 15 other base known to be useful in acylation reactions. The reaction is performed in a solvent solvent such as THF, dioxane, toluene, dichloromethane, DMF, NMP or a mixture of two or more of these. The reaction is performed between 0 °C and 80 °C, preferably between 20 °C and 40 °C. When the acylation is complete, the product is isolated by extraction, filtration, chromatography or other methods known to those skilled in the art.

20

The general procedure (A) is further illustrated in the following example:

0102-0000-1020 Example 9 (General Procedure (A)) PEM

1H-Benzotriazole-5-carboxylic acid phenylamide



- 25 Benzotriazole-5-carboxylic acid (856 mg), HOAt (715 mg) and EDAC (1.00 g) were dissolved in DMF (17.5 mL) and the mixture was stirred at room temperature 1 hour. A 0.5 mL aliquot of this mixture was added to aniline (13.7 µL, 0.15 mmol) and the resulting mixture was vigorously shaken at room temperature for 16 hours. 1N hydrochloric acid (2 mL) and ethyl acetate (1 mL) were added and the mixture was vigorously shaken at room temperature for 2

hours. The organic phase was isolated and concentrated *in vacuo* to afford the title compound.

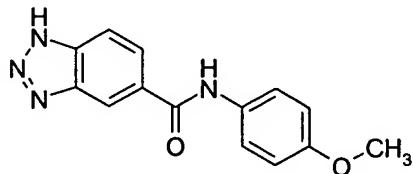
HPLC-MS (Method B): m/z: 239 (M+1); Rt = 3.93 min.

5

The compounds in the following examples were similarly made. Optionally, the compounds may be isolated by filtration or by chromatography.

0102-0000-1019Example 10 (General Procedure (A))PEM

10 1*H*-Benzotriazole-5-carboxylic acid (4-methoxyphenyl)amide

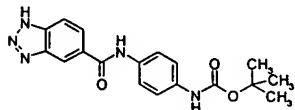


HPLC-MS (Method A): m/z: 269 (M+1) & 291 (M+23); Rt = 2.41 min

HPLC-MS (Method B): m/z: 239 (M+1); Rt = 3.93 min.

15 0102-0000-1021Example 11 (General Procedure (A))PEM

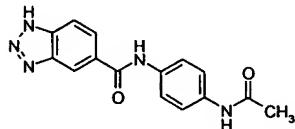
{4-[(1*H*-Benzotriazole-5-carbonyl)amino]phenyl}carbamic acid *tert*-butyl ester



HPLC-MS (Method B): m/z: 354 (M+1); Rt = 4.58 min.

20 0102-0000-1022Example 12 (General Procedure (A))PEM

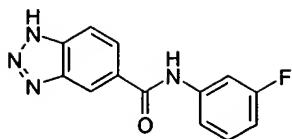
1*H*-Benzotriazole-5-carboxylic acid (4-acetylaminophenyl)amide



HPLC-MS (Method B): m/z: 296 (M+1); Rt = 3.32 min.

25 0102-0000-1023Example 13 (General Procedure (A))PEM

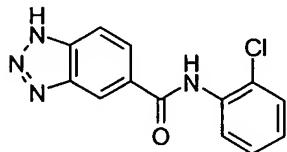
1*H*-Benzotriazole-5-carboxylic acid (3-fluorophenyl)amide



HPLC-MS (Method B): m/z: 257 (M+1); Rt = 4.33 min.

0102-0000-1024 Example 14 (General Procedure (A)) PEM

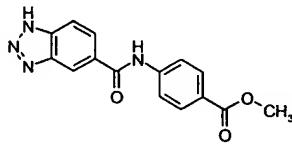
- 5 1*H*-Benzotriazole-5-carboxylic acid (2-chlorophenyl)amide



HPLC-MS (Method B): m/z: 273 (M+1); Rt = 4.18 min.

0102-0000-1025 Example 15 (General Procedure (A)) PEM

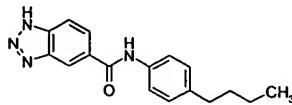
- 10 4-[(1*H*-Benzotriazole-5-carbonyl)amino]benzoic acid methyl ester



HPLC-MS (Method A): m/z: 297 (M+1); Rt : 2.60 min. HPLC-MS (Method B): m/z: 297 (M+1);
Rt = 4.30 min.

0102-0000-1026 Example 16 (General Procedure (A)) PEM

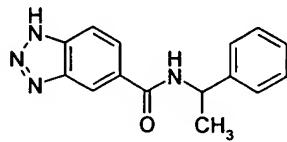
- 15 1*H*-Benzotriazole-5-carboxylic acid (4-butylphenyl)amide



HPLC-MS (Method B): m/z: 295 (M+1); Rt = 5.80 min.

0102-0000-1027 Example 17 (General Procedure (A)) PEM

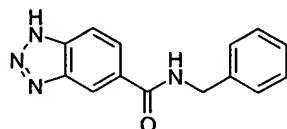
- 20 1*H*-Benzotriazole-5-carboxylic acid (1-phenylethyl)amide



HPLC-MS (Method B): m/z: 267 (M+1); Rt = 4.08 min.

0102-0000-1028 Example 18 (General Procedure (A))PEM

1H-Benzotriazole-5-carboxylic acid benzylamide

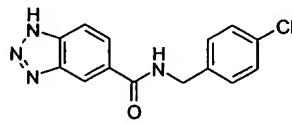


HPLC-MS (Method B): m/z: 253 (M+1); Rt = 3.88 min.

5

0102-0000-1029 Example 19 (General Procedure (A))PEM

1H-Benzotriazole-5-carboxylic acid 4-chlorobenzylamide

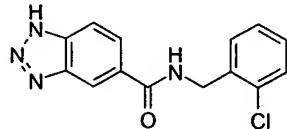


HPLC-MS (Method B): m/z: 287 (M+1); Rt = 4.40 min.

10

0102-0000-1030 Example 20 (General Procedure (A))PEM

1H-Benzotriazole-5-carboxylic acid 2-chlorobenzylamide

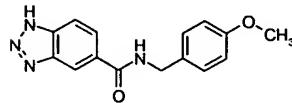


HPLC-MS (Method B): m/z: 287 (M+1); Rt = 4.25 min.

15

0102-0000-1031 Example 21 (General Procedure (A))PEM

1H-Benzotriazole-5-carboxylic acid 4-methoxybenzylamide

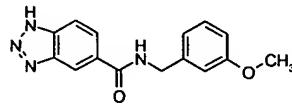


HPLC-MS (Method B): m/z: 283 (M+1); Rt = 3.93 min.

20

0102-0000-1032 Example 22 (General Procedure (A))PEM

1H-Benzotriazole-5-carboxylic acid 3-methoxybenzylamide

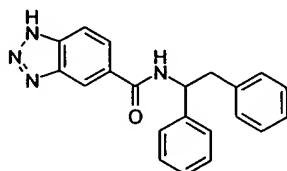


HPLC-MS (Method B): m/z: 283 (M+1); Rt = 3.97 min.

25

0102-0000-1033 Example 23 (General Procedure (A))PEM

1H-Benzotriazole-5-carboxylic acid (1,2-diphenylethyl)amide

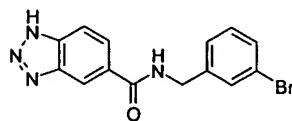


HPLC-MS (Method B): m/z: 343 (M+1); Rt = 5.05 min.

5

0102-0000-1034 Example 24 (General Procedure (A))PEM

1H-Benzotriazole-5-carboxylic acid 3-bromobenzylamide

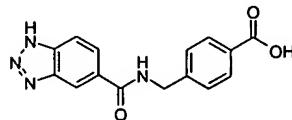


HPLC-MS (Method B): m/z: 331 (M+1); Rt = 4.45 min.

10

0102-0000-1035 Example 25 (General Procedure (A))PEM

4-{{(1*H*-Benzotriazole-5-carbonyl)amino}methyl}benzoic acid

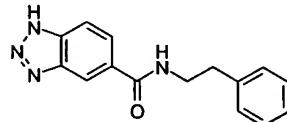


HPLC-MS (Method B): m/z: 297 (M+1); Rt = 3.35 min.

15

0102-0000-1036 Example 26 (General Procedure (A))PEM

1H-Benzotriazole-5-carboxylic acid phenethylamide

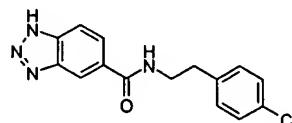


HPLC-MS (Method B): m/z: 267 (M+1); Rt = 4.08 min.

20

0102-0000-1037 Example 27 (General Procedure (A))PEM

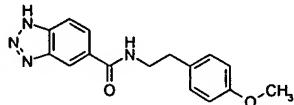
1H-Benzotriazole-5-carboxylic acid [2-(4-chlorophenyl)ethyl]amide



HPLC-MS (Method B): m/z: 301 (M+1); Rt = 4.50 min.

0102-0000-1038 Example 28 (General Procedure (A))PEM

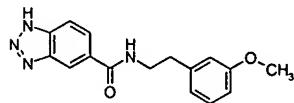
1H-Benzotriazole-5-carboxylic acid [2-(4-methoxyphenyl)ethyl]amide



5 HPLC-MS (Method B): m/z: 297 (M+1); Rt = 4.15 min.

0102-0000-1039 Example 29 (General Procedure (A))PEM

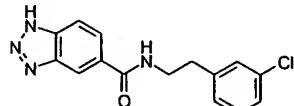
1H-Benzotriazole-5-carboxylic acid [2-(3-methoxyphenyl)ethyl]amide



10 HPLC-MS (Method B): m/z: 297 (M+1); Rt = 4.13 min.

0102-0000-1040 Example 30 (General Procedure (A))PEM

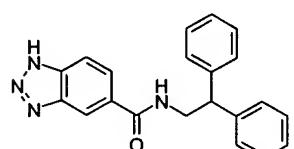
1H-Benzotriazole-5-carboxylic acid [2-(3-chlorophenyl)ethyl]amide



15 HPLC-MS (Method B): m/z: 301 (M+1); Rt = 4.55 min.

0102-0000-1041 Example 31 (General Procedure (A))PEM

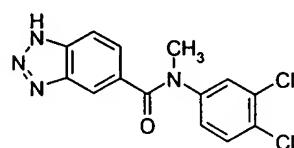
1H-Benzotriazole-5-carboxylic acid (2,2-diphenylethyl)amide



20 HPLC-MS (Method B): m/z: 343 (M+1); Rt = 5.00 min.

0102-0000-1042 Example 32 (General Procedure (A))PEM

1H-Benzotriazole-5-carboxylic acid (3,4-dichlorophenyl)methylamide

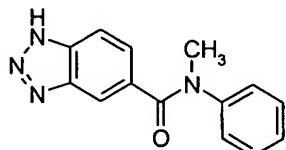


100

HPLC-MS (Method B): m/z: 321 (M+1); Rt = 4.67 min.

0102-0000-1043 Example 33 (General Procedure (A)) PEM

1H-Benzotriazole-5-carboxylic acid methylphenylamide

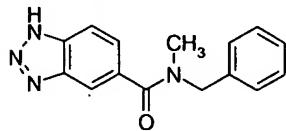


5

HPLC-MS (Method B): m/z: 253 (M+1); Rt = 3.82 min.

0102-0000-1044 Example 34 (General Procedure (A)) PEM

1H-Benzotriazole-5-carboxylic acid benzylmethylamide

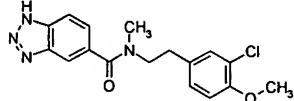


10

HPLC-MS (Method B): m/z: 267 (M+1); Rt = 4.05 min.

0102-0000-1045 Example 35 (General Procedure (A)) PEM

1H-Benzotriazole-5-carboxylic acid [2-(3-chloro-4-methoxyphenyl)ethyl]methyl-amide

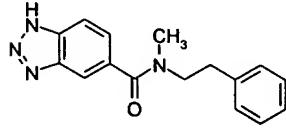


15

HPLC-MS (Method B): m/z: 345 (M+1); Rt = 4.37 min.

0102-0000-1046 Example 36 (General Procedure (A)) PEM

1H-Benzotriazole-5-carboxylic acid methylphenethylamide

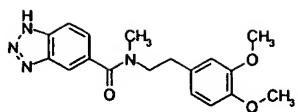


20

HPLC-MS (Method B): m/z: 281 (M+1); Rt = 4.15 min.

0102-0000-1047 Example 37 (General Procedure (A)) PEM

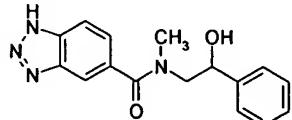
1H-Benzotriazole-5-carboxylic acid [2-(3,4-dimethoxyphenyl)ethyl]methylamide



HPLC-MS (Method B): m/z: 341 (M+1); Rt = 3.78 min;

0102-0000-1048 Example 38 (General Procedure (A)) PEM

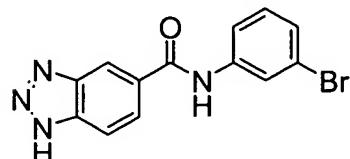
- 5 **1H-Benzotriazole-5-carboxylic acid (2-hydroxy-2-phenylethyl)methylamide**



HPLC-MS (Method B): m/z: 297 (M+1); Rt = 3.48 min.

Example 39 (General procedure (A))

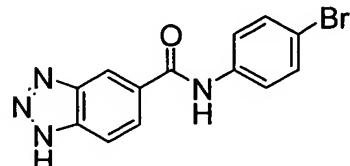
- 10 **1H-Benzotriazole-5-carboxylic acid (3-bromophenyl)amide**



HPLC-MS (Method A): m/z: 317 (M+1); Rt = 3.19 min.

Example 40 (General procedure (A))

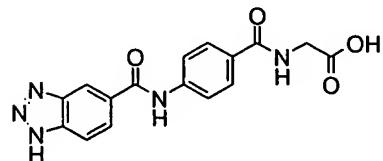
- 15 **1H-Benzotriazole-5-carboxylic acid (4-bromophenyl)amide**



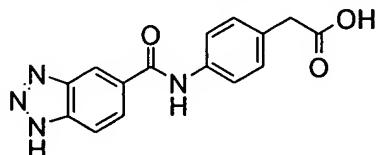
HPLC-MS (Method A): m/z: 317 (M+1); Rt = 3.18 min.

Example 41 (General procedure (A))

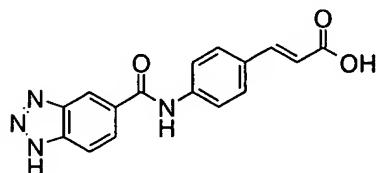
- 20 **{4-[(1H-Benzotriazole-5-carbonyl)amino]benzoylamino}acetic acid**



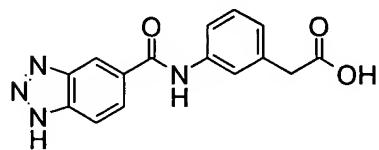
HPLC-MS (Method A): m/z: 340 (M+1); Rt = 1.71 min.

Example 42 (General procedure (A))**{4-[(1H-Benzotriazole-5-carbonyl)amino]phenyl}acetic acid**

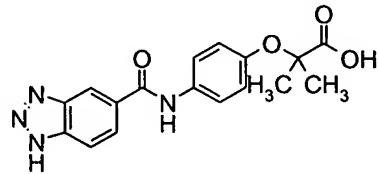
- 5 HPLC-MS (Method A): m/z: 297 (M+1); Rt = 2.02 min.

Example 43 (General procedure (A))**3-{4-[(1H-Benzotriazole-5-carbonyl)amino]phenyl}acrylic acid**

- 10 HPLC-MS (Method A): m/z: 309 (M+1); Rt = 3.19 min.

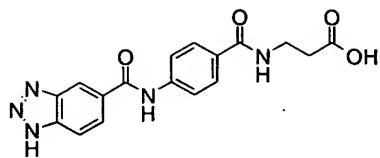
Example 44 (General procedure (A))**{3-[(1H-Benzotriazole-5-carbonyl)amino]phenyl}acetic acid**

- 15 HPLC-MS (Method A): m/z: 297 (M+1); Rt = 2.10 min.

Example 45 (General procedure (A))**2-{4-[(1H-Benzotriazole-5-carbonyl)amino]phenoxy}-2-methylpropionic acid**

- 20 HPLC-MS (Method A): m/z: 341 (M+1); Rt = 2.42 min.

Example 46 (General procedure (A))**3-{4-[(1H-Benzotriazole-5-carbonyl)amino]benzoylamino}propionic acid**



HPLC-MS (Method A): m/z: 354 (M+1); Rt = 1.78 min.

Example 47 (General procedure (A))

- 5 3-{[(1H-Benzotriazole-5-carbonyl)amino]phenyl}propionic acid



HPLC-MS (Method A): m/z: 311 (M+1); Rt = 2.20 min.

Example 48 (General procedure (A))

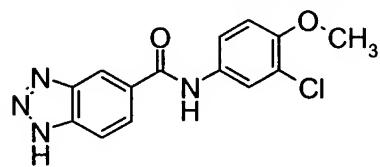
- 10 1H-Benzotriazole-5-carboxylic acid (4-benzyloxyphenyl)amide



HPLC-MS (Method A): m/z: 345 (M+1); Rt = 3.60 min.

Example 49 (General procedure (A))

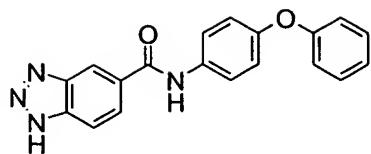
- 15 1H-Benzotriazole-5-carboxylic acid (3-chloro-4-methoxyphenyl)amide



HPLC-MS (Method A): m/z: 303 (M+1); Rt = 2.88 min.

Example 50 (General procedure (A))

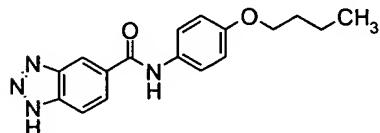
- 20 1H-Benzotriazole-5-carboxylic acid (4-phenoxyphenyl)amide



HPLC-MS (Method A): m/z: 331 (M+1); Rt = 3.62 min.

Example 51 (General procedure (A))

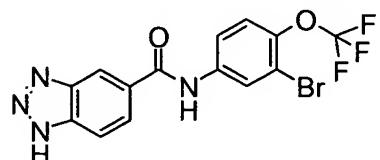
- 5 1H-Benzotriazole-5-carboxylic acid (4-butoxyphenyl)amide



HPLC-MS (Method A): m/z: 311 (M+1); Rt = 3.59 min.

Example 52 (General procedure (A))

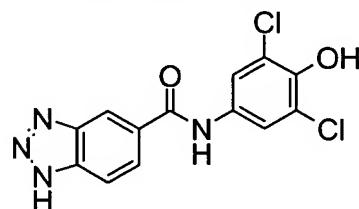
- 10 1H-Benzotriazole-5-carboxylic acid (3-bromo-4-trifluoromethoxyphenyl)amide



HPLC-MS (Method A): m/z: 402 (M+1); Rt = 3.93 min.

Example 53 (General procedure (A))

- 15 1H-Benzotriazole-5-carboxylic acid (3,5-dichloro-4-hydroxyphenyl)amide

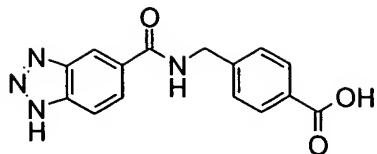


HPLC-MS (Method A): m/z: 323 (M+1); Rt = 2.57 min.

Example 54 (General procedure (A))

- 20 4-{[(1H-Benzotriazole-5-carbonyl)amino]methyl}benzoic acid

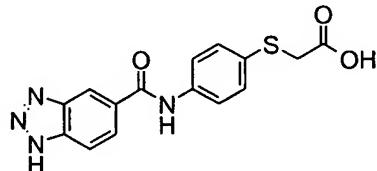
105



HPLC-MS (Method A): m/z: 297 (M+1); Rt = 1.86 min.

Example 55 (General procedure (A))

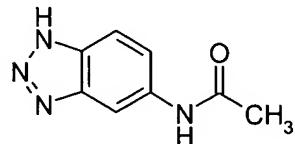
- 5 {4-[(1H-Benzotriazole-5-carbonyl)amino]phenylsulfanyl}acetic acid



HPLC-MS (Method A): m/z: 329 (M+1); Rt = 2.34 min.

Example 56

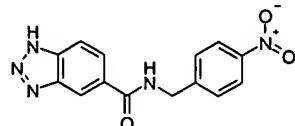
- 10 N-(1H-Benzotriazol-5-yl)acetamide



HPLC-MS (Method A): m/z: 177 (M+1); Rt = 0.84 min.

Example 57 (General Procedure (A))

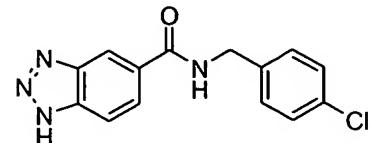
- 15 1H-Benzotriazole-5-carboxylic acid 4-nitrobenzylamide



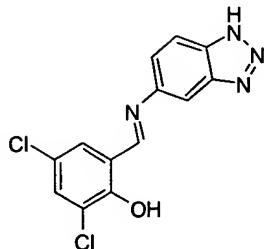
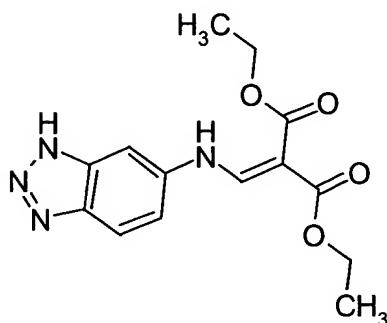
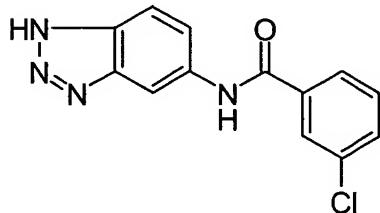
The following compound is prepared according to general procedure (N) as described below:

Example 58 (General procedure (N))

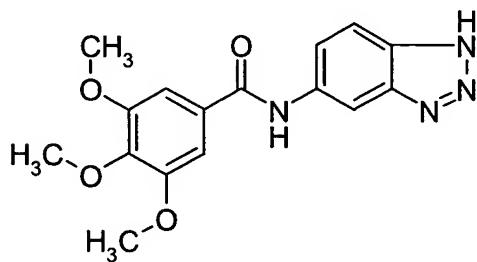
- 20 1H-Benzotriazole-5-carboxylic acid 4-chlorobenzylamide



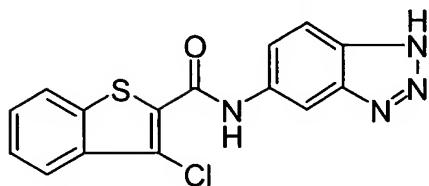
HPLC-MS (Method B): m/z: 287 (M+1); Rt = 4.40 min.

Example 59 2-[(1H-Benzotriazol-5-ylimino)methyl]-4,6-dichlorophenol**5 Example 60 Diethyl 2-[(1H-benzotriazol-6-ylamino)methylidene]malonate****Example 61 N1-(1H-Benzotriazol-5-yl)-3-chlorobenzamide**

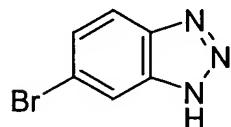
10

Example 62 N1-(1H-Benzotriazol-5-yl)-3,4,5-trimethoxybenzamide

Example 63 N2-(1H-Benzotriazol-5-yl)-3-chlorobenzo[b]thiophene-2-carboxamide

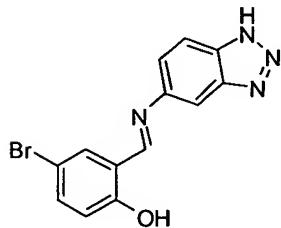
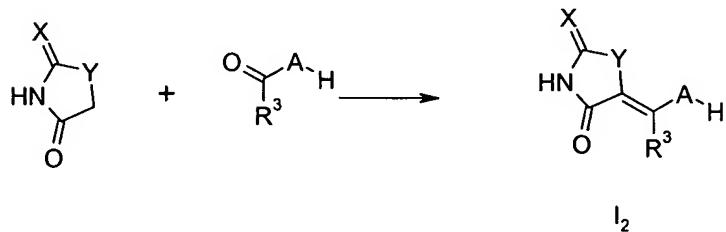


Example 64 6-Bromo-1H-benzotriazole



5

Example 65 2-[(1H-Benzotriazol-5-ylimino)methyl]-4-bromophenol

10 General procedure (B) for preparation of compounds of general formula I₂:

wherein X, Y, A and R³ are as defined above and A is optionally substituted with up to four substituents R⁷, R⁸, R⁹, and R¹⁰ as defined above.

15

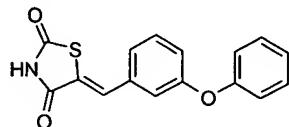
The chemistry is well known (eg Lohray et al., *J. Med. Chem.*, **1999**, *42*, 2569-81) and is generally performed by reacting a carbonyl compound (aldehyde or ketone) with the heterocyclic ring (eg thiazolidine-2,4-dione (X = O; Y = S), rhodanine (X = Y = S) and

hydantoin ($X = O$; $Y = NH$) in the presence of a base, such as sodium acetate, potassium acetate, ammonium acetate, piperidinium benzoate or an amine (eg piperidine, triethylamine and the like) in a solvent (eg acetic acid, ethanol, methanol, DMSO, DMF, NMP, toluene, benzene) or in a mixture of two or more of these solvents. The reaction is performed at room
5 temperature or at elevated temperature, most often at or near the boiling point of the mixture. Optionally, azeotropic removal of the formed water can be done.

This general procedure (B) is further illustrated in the following example:

Example 66 (General procedure (B))

- 10 5-(3-Phenoxybenzylidene)thiazolidine-2,4-dione



A solution of thiazolidine-2,4-dione (90%, 78 mg, 0.6 mmol) and ammonium acetate (92 mg, 1.2 mmol) in acetic acid (1 mL) was added to 3-phenoxybenzaldehyde (52 μ L, 0.6 mmol) and the resulting mixture was shaken at 115 °C for 16 hours. After cooling, the mixture was

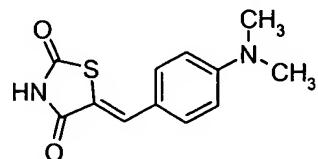
- 15 concentrated *in vacuo* to afford the title compound.

HPLC-MS (Method A): m/z: 298 (M+1); Rt = 4.54 min.

The compounds in the following examples were similarly prepared. Optionally, the
20 compounds can be further purified by filtration and washing with water, ethanol and / or heptane instead of concentration *in vacuo*. Also optionally the compounds can be purified by washing with ethanol, water and/or heptane, or by chromatography, such as preparative HPLC.

Example 67 (General procedure (B))

- 25 5-(4-Dimethylaminobenzylidene)thiazolidine-2,4-dione

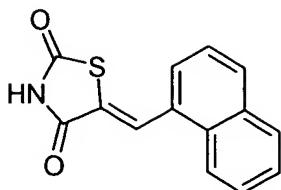


HPLC-MS (Method C): m/z: 249 (M+1); Rt = 4.90 min

Example 68 (General procedure (B))

- 30 5-Naphthalen-1-ylmethylenethiazolidine-2,4-dione

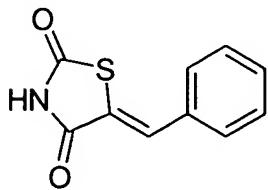
109



HPLC-MS (Method A): m/z: 256 (M+1); Rt = 4.16 min.

Example 69 (General procedure (B))

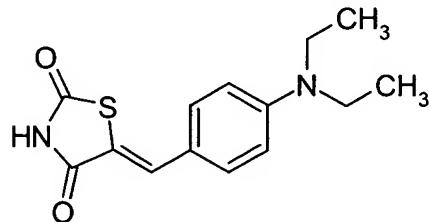
- 5 5-Benzylidene-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 206 (M+1); Rt = 4.87 min.

Example 70 (General procedure (B))

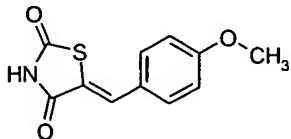
- 10 5-(4-Diethylaminobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 277 (M+1); Rt = 4.73 min.

Example 71 (General procedure (B))

- 15 5-(4-Methoxy-benzylidene)-thiazolidine-2,4-dione

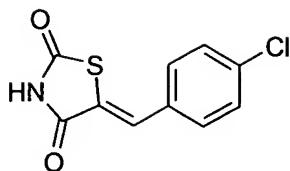


HPLC-MS (Method A): m/z: 263 (M+1); Rt = 4.90 min.

Example 72 (General procedure (B))

- 20 5-(4-Chloro-benzylidene)-thiazolidine-2,4-dione

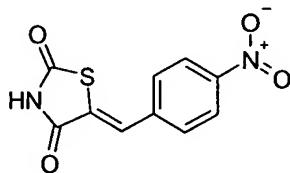
110



HPLC-MS (Method A): m/z: 240 (M+1); Rt = 5,53 min.

Example 73 (General procedure (B))

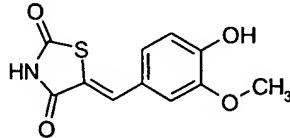
- 5 5-(4-Nitro-benzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 251 (M+1); Rt = 4,87 min.

Example 74 (General procedure (B))

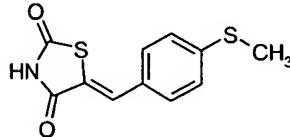
- 10 5-(4-Hydroxy-3-methoxy-benzylidene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 252 (M+1); Rt = 4,07 min.

Example 75 (General procedure (B))

- 15 5-(4-Methylsulfanylbenzylidene)thiazolidine-2,4-dione

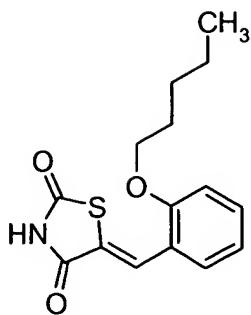


HPLC-MS (Method A): m/z: 252 (M+1); Rt = 5,43 min.

Example 76 (General procedure (B))

- 20 5-(2-Pentyloxybenzylidene)thiazolidine-2,4-dione

111



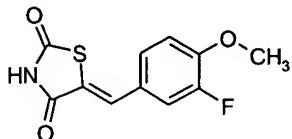
HPLC-MS (Method C): m/z: 292 (M+1); Rt = 4.75 min.

¹H NMR (DMSO-d₆): δ = 0.90 (3H, t), 1.39 (4H, m), 1.77 (2H, p), 4.08 (2H, t), 7.08 (1H, t), 7.14 (1H, d), 7.43 (2H, m), 8.03 (1H, s), 12.6 (1H, bs).

5

Example 77 (General procedure (B))

5-(3-Fluoro-4-methoxybenzylidene)thiazolidine-2,4-dione

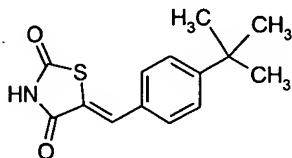


HPLC-MS (Method A): m/z: 354 (M+1); Rt = 4.97 min.

10

Example 78 (General procedure (B))

5-(4-tert-Butylbenzylidene)thiazolidine-2,4-dione

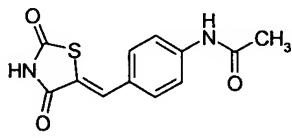


HPLC-MS (Method A): m/z: 262 (M+1); Rt = 6.70 min.

15

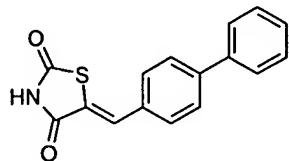
Example 79 (General procedure (B))

N-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenyl]acetamide



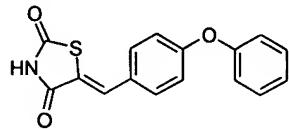
HPLC-MS (Method A): m/z: 263 (M+1); Rt = 3.90 min.

20

Example 80 (General procedure (B))**5-Biphenyl-4-ylmethylenethiazolidine-2,4-dione**

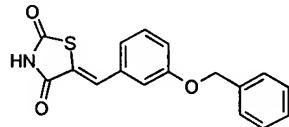
HPLC-MS (Method A): m/z: 282 (M+1); Rt = 4,52 min.

5

Example 81 (General procedure (B))**5-(4-Phenoxybenzylidene)thiazolidine-2,4-dione**

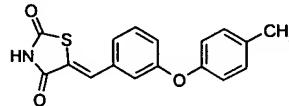
HPLC-MS (Method A): m/z: 298 (M+1); Rt = 6,50 min.

10

Example 82 (General procedure (B))**5-(3-Benzylxybenzylidene)thiazolidine-2,4-dione**

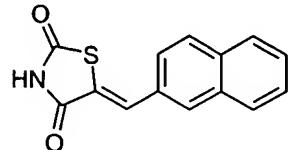
HPLC-MS (Method A): m/z: 312 (M+1); Rt = 6,37 min.

15

Example 83 (General procedure (B))**5-(3-p-Tolyloxybenzylidene)thiazolidine-2,4-dione**

HPLC-MS (Method A): m/z: 312 (M+1); Rt = 6,87 min.

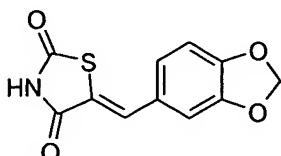
20

Example 84 (General procedure (B))**5-Naphthalen-2-ylmethylenethiazolidine-2,4-dione**

HPLC-MS (Method A): m/z: 256 (M+1); Rt = 4.15 min.

Example 85 (General procedure (B))

5-Benzo[1,3]dioxol-5-ylmethylenethiazolidine-2,4-dione

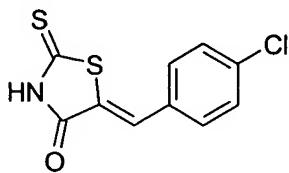


5

HPLC-MS (Method A): m/z: 250 (M+1), Rt = 3.18 min.

Example 86 (General procedure (B))

5-(4-Chlorobenzylidene)-2-thioxothiazolidin-4-one

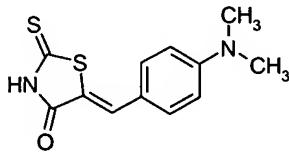


10

HPLC-MS (Method A): m/z: 256 (M+1); Rt = 4.51 min.

Example 87 (General procedure (B))

5-(4-Dimethylaminobenzylidene)-2-thioxothiazolidin-4-one

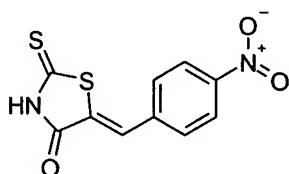


15

HPLC-MS (Method A): m/z: 265 (M+1); Rt = 5.66 min.

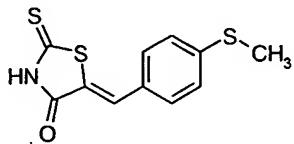
Example 88 (General procedure (B))

5-(4-Nitrobenzylidene)-2-thioxothiazolidin-4-one



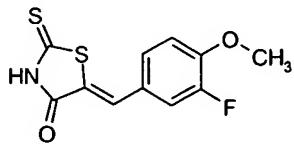
20

HPLC-MS (Method A): m/z: 267 (M+1); Rt = 3.94 min.

Example 89 (General procedure (B))**5-(4-Methylsulfanylbenzylidene)-2-thioxothiazolidin-4-one**

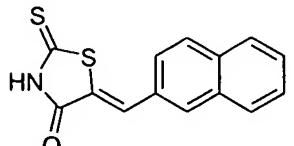
HPLC-MS (Method A): m/z: 268 (M+1); Rt = 6,39 min.

5

Example 90 (General procedure (B))**5-(3-Fluoro-4-methoxybenzylidene)-2-thioxothiazolidin-4-one**

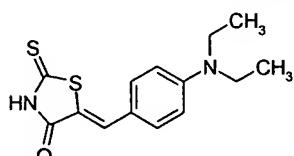
HPLC-MS (Method A): m/z: 270 (M+1); Rt = 5,52 min.

10

Example 91 (General procedure (B))**5-Naphthalen-2-ylmethylene-2-thioxothiazolidin-4-one**

HPLC-MS (Method A): m/z: 272 (M+1); Rt = 6,75 min.

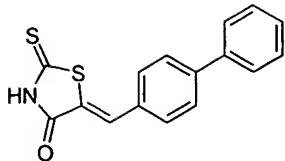
15

Example 92 (General procedure (B))**5-(4-Diethylaminobenzylidene)-2-thioxothiazolidin-4-one**

HPLC-MS (Method A): m/z: 293 (M+1); Rt = 5,99 min.

20

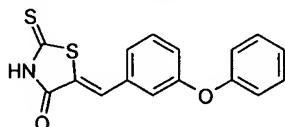
Example 93 (General procedure (B))**5-Biphenyl-4-ylmethylene-2-thioxothiazolidin-4-one**



HPLC-MS (Method A): m/z: 298 (M+1); Rt = 7,03 min.

Example 94 (General procedure (B))

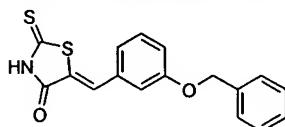
- 5 5-(3-Phenoxybenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 314 (M+1); Rt = 6,89 min.

Example 95 (General procedure (B))

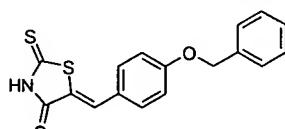
- 10 5-(3-Benzylbenzylidene)-2-thioxothiazolidin-4-one



HPLC-MS (Method A): m/z: 328 (M+1); Rt = 6,95 min.

Example 96 (General procedure (B))

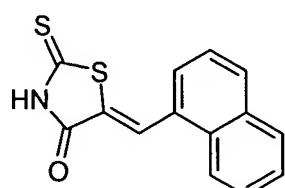
- 15 5-(4-Benzylbenzylidene)-2-thioxothiazolidin-4-one



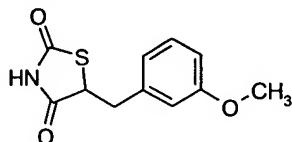
HPLC-MS (Method A): m/z: 328 (M+1); RT = 6,89 min.

Example 97 (General procedure (B))

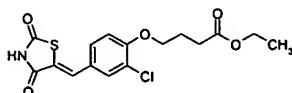
- 20 5-Naphthalen-1-ylmethylene-2-thioxothiazolidin-4-one



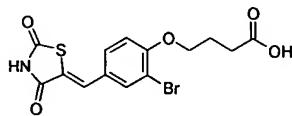
HPLC-MS (Method A): m/z: 272 (M+1); Rt = 6,43 min.

Example 98 (General procedure (B))**5-(3-Methoxybenzyl)thiazolidine-2,4-dione**

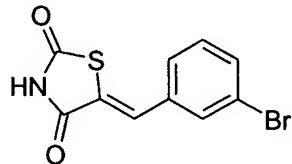
- 5 HPLC-MS (Method A): m/z: 236 (M+1); Rt = 3.05 min.

Example 99 (General procedure (D))**4-[2-Chloro-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid ethyl ester**

- 10 HPLC-MS (Method A): m/z: 392 (M+23), Rt = 4.32 min.

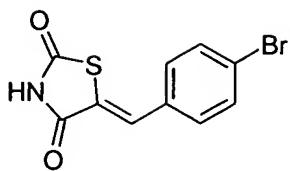
Example 100 (General procedure (D))**4-[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)-phenoxy]-butyric acid**

- 15 HPLC-MS (Method A): m/z: 410 (M+23); Rt = 3.35 min.

Example 101 (General procedure (B))**5-(3-Bromobenzylidene)thiazolidine-2,4-dione**

- 20 HPLC-MS (Method A): m/z: 285 (M+1); Rt = 4.01 min.

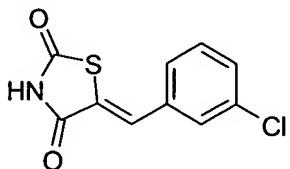
Example 102 (General procedure (B))**5-(4-Bromobenzylidene)thiazolidine-2,4-dione**



HPLC-MS (Method A): m/z: 285 (M+1); Rt = 4.05 min.

Example 103 (General procedure (B))

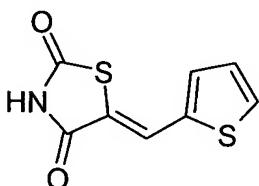
- 5 5-(3-Chlorobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 240 (M+1); Rt = 3.91 min.

Example 104 (General procedure (B))

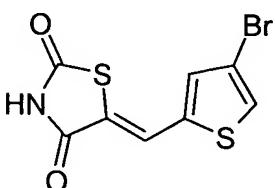
- 10 5-Thiophen-2-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 212 (M+1); Rt = 3.09 min.

Example 105 (General procedure (B))

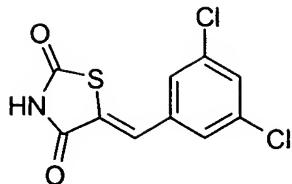
- 15 5-(4-Bromothiophen-2-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 291 (M+1); Rt = 3.85 min.

Example 106 (General procedure (B))

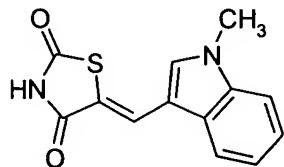
- 20 5-(3,5-Dichlorobenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 274 (M+1); Rt = 4.52 min.

Example 107 (General procedure (B))

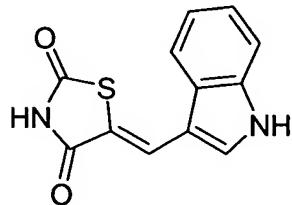
- 5 5-(1-Methyl-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 259 (M+1); Rt = 3.55 min.

Example 108 (General procedure (B))

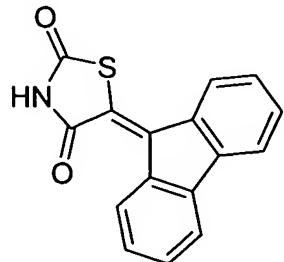
- 10 5-(1H-Indol-3-ylmethylene)thiazolidine-2,4-dione



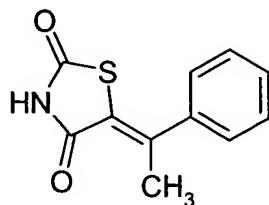
HPLC-MS (Method A): m/z: 245 (M+1); Rt = 2.73 min.

Example 109 (General procedure (B))

- 15 5-Fluoren-9-ylidenethiazolidine-2,4-dione

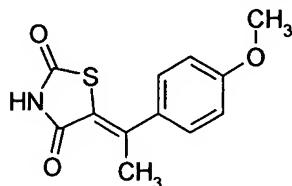


HPLC-MS (Method A): m/z: 280 (M+1); Rt = 4.34 min.

Example 110 (General procedure (B))**5-(1-Phenylethylidene)thiazolidine-2,4-dione**

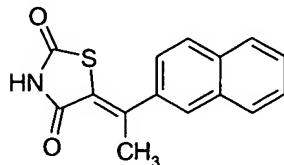
HPLC-MS (Method A): m/z: 220 (M+1); Rt = 3,38 min.

5

Example 111 (General procedure (B))**5-[1-(4-Methoxyphenyl)-ethylidene]-thiazolidine-2,4-dione**

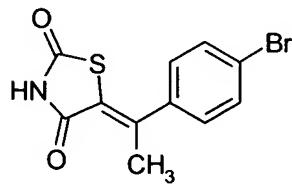
HPLC-MS (Method A): m/z: 250 (M+1); Rt = 3.55 min.

10

Example 112 (General procedure (B))**5-(1-Naphthalen-2-yl-ethylidene)-thiazolidine-2,4-dione**

HPLC-MS (Method A): m/z: 270 (M+1); Rt = 4,30 min.

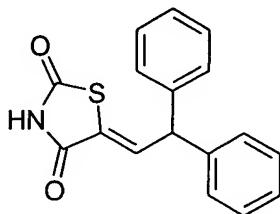
15

Example 113 (General procedure (B))**5-[1-(4-Bromophenyl)-ethylidene]-thiazolidine-2,4-dione**

HPLC-MS (Method A): m/z: 300 (M+1); Rt = 4,18 min.

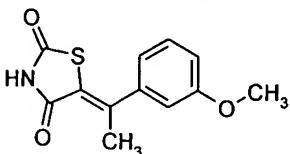
20

120

Example 114 (General procedure (B))**5-(2,2-Diphenylethylidene)-thiazolidine-2,4-dione**

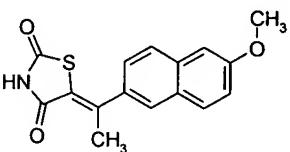
HPLC-MS (Method A): m/z: 296 (M+1); Rt = 4,49 min.

5

Example 115 (General procedure (B))**5-[1-(3-Methoxyphenyl)-ethylidene]-thiazolidine-2,4-dione**

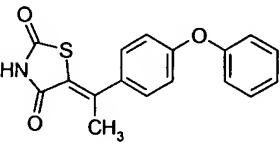
HPLC-MS (Method A): m/z: 250 (M+1); Rt = 3,60 min.

10

Example 116 (General procedure (B))**5-[1-(6-Methoxynaphthalen-2-yl)-ethylidene]-thiazolidine-2,4-dione**

HPLC-MS (Method A): m/z: 300 (M+1); Rt = 4,26 min.

15

Example 117 (General procedure (B))**5-[1-(4-Phenoxyphenyl)-ethylidene]-thiazolidine-2,4-dione**

HPLC-MS (Method A): m/z: 312 (M+1); Rt = 4,68 min.

20

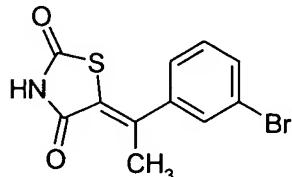
Example 118 (General procedure (B))**5-[1-(3-Fluoro-4-methoxyphenyl)ethylidene]thiazolidine-2,4-dione**



HPLC-MS (Method A): m/z: 268 (M+1); Rt = 3,58 min.

Example 119 (General procedure (B))

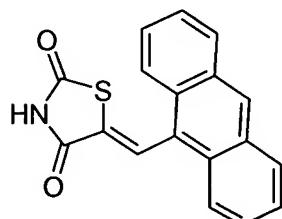
- 5 5-[1-(3-Bromophenyl)-ethylidene]-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 300 (M+1); Rt = 4,13 min.

Example 120 (General procedure (B))

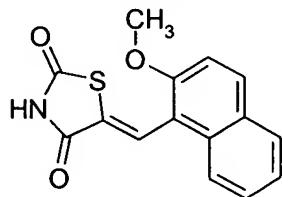
- 10 5-Anthracen-9-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 306 (M+1); Rt = 4,64 min.

Example 121 (General procedure (B))

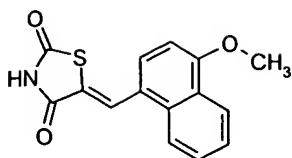
- 15 5-(2-Methoxynaphthalen-1-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 286 (M+1); Rt = 4,02 min.

Example 122 (General procedure (B))

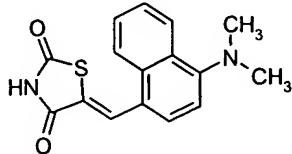
- 20 5-(4-Methoxynaphthalen-1-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 286 (M+1); Rt = 4,31 min.

Example 123 (General procedure (B))

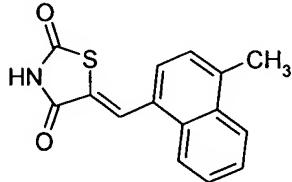
- 5 5-(4-Dimethylaminonaphthalen-1-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 299 (M+1); Rt = 4,22 min.

Example 124 (General procedure (B))

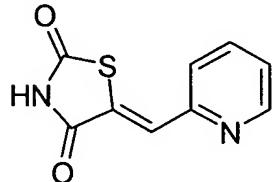
- 10 5-(4-Methylnaphthalen-1-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 270 (M+1); Rt = 4,47 min.

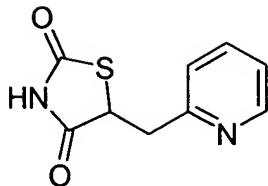
Example 125 (General procedure (B))

- 15 5-Pyridin-2-ylmethylene-thiazolidine-2,4-dione



Example 126

- 5-Pyridin-2-ylmethyl-thiazolidine-2,4-dione



- 5-Pyridin-2-ylmethylene-thiazolidine-2,4-dione (5 g) in tetrahydrofuran (300 ml) was added 10% Pd/C (1 g) and the mixture was hydrogenated at ambient pressure for 16 hours. More 10% Pd/C (5 g) was added and the mixture was hydrogenated at 50 psi for 16 hours. After 5 filtration and evaporation *in vacuo*, the residue was purified by column chromatography eluting with a mixture of ethyl acetate and heptane (1:1). This afforded the title compound (0.8 g, 16%) as a solid.

TLC: $R_f = 0.30$ (SiO_2 ; EtOAc: heptane 1:1)

10

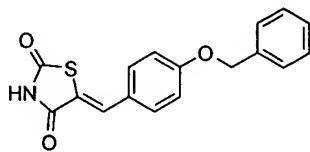
Example 127 (General procedure (B))

5-(1H-Imidazol-4-ylmethylene)-thiazolidine-2,4-dione



15 Example 128 (General procedure (B))

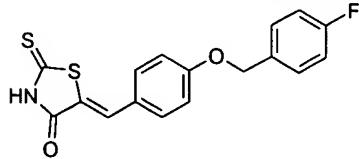
5-(4-Benzyloxy-benzylidene)-thiazolidine-2,4-dione

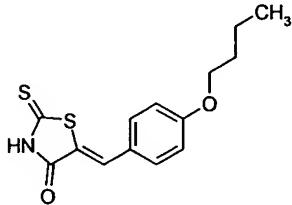


HPLC-MS (Method A): m/z: 6,43 min ; 99 % (2A)

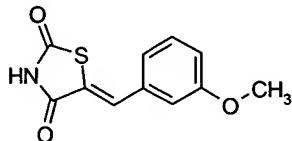
20 Example 129 (General procedure (B))

5-[4-(4-Fluorobenzyloxy)benzylidene]-2-thioxothiazolidin-4-one

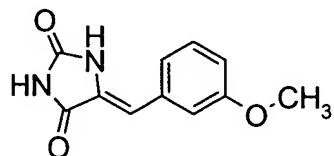


Example 130 (General procedure (B))**5-(4-Butoxybenzylidene)-2-thioxothiazolidin-4-one**

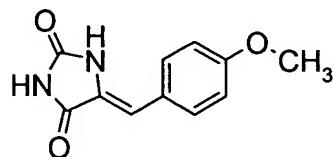
5

Example 131 (General procedure (B))**5-(3-Methoxybenzylidene)thiazolidine-2,4-dione**

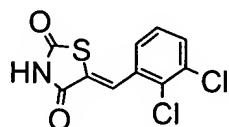
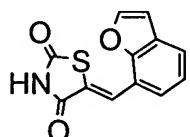
10 HPLC-MS (Method A): m/z: 236 (M+1); Rt = 4.97 min

Example 132 (General procedure (B))15 **5-(3-Methoxybenzylidene)imidazolidine-2,4-dione**

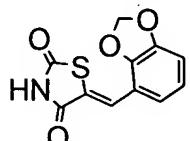
HPLC-MS (Method A): m/z: 219 (M+1); Rt = 2.43 min.

Example 133 (General procedure (B))20 **5-(4-Methoxybenzylidene)imidazolidine-2,4-dione**

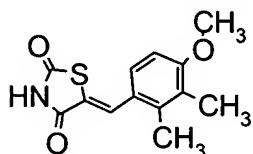
HPLC-MS (Method A): m/z: 219 (M+1); Rt = 2.38 min.

Example 134 (General procedure (B))**5-(2,3-Dichlorobenzylidene)thiazolidine-2,4-dione****5 Example 135 (General procedure (B))****5-Benzofuran-7-ylmethylenethiazolidine-2,4-dione**

HPLC-MS (Method C): m/z: 247 (M+1); Rt = 4,57 min.

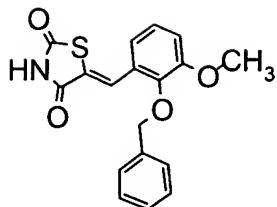
10 Example 136 (General procedure (B))**5-Benzo[1,3]dioxol-4-ylmethylenethiazolidine-2,4-dione**

HPLC-MS (Method C): m/z: 250 (M+1); Rt = 4,00 min.

15 Example 137 (General procedure (B))**5-(4-Methoxy-2,3-dimethylbenzylidene)thiazolidine-2,4-dione**

HPLC-MS (Method C): m/z: 264 (M+1); Rt = 5,05 min.

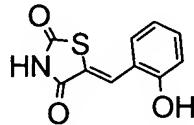
20 Example 138 (General procedure (B))**5-(2-Benzylxy-3-methoxybenzylidene)thiazolidine-2,4-dione**



HPLC-MS (Method C): m/z: 342 (M+1); Rt = 5.14 min.

Example 139 (General procedure (B))

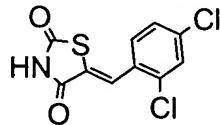
- 5 5-(2-Hydroxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 222 (M+1); Rt = 3.67 min.

Example 140 (General procedure (B))

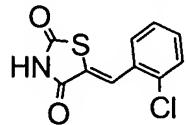
- 10 5-(2,4-Dichlorobenzylidene)thiazolidine-2,4-dione



¹H-NMR (DMSO-d₆): 7.60 (2H, "s"), 7.78 (1H, s), 7.82 (1H, s).

Example 141 (General procedure (B))

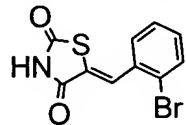
- 15 5-(2-Chlorobenzylidene)thiazolidine-2,4-dione



¹H-NMR (DMSO-d₆): 7.40 (1H, t), 7.46 (1H, t), 7.57 (1H, d), 7.62 (1H, d), 7.74 (1H, s).

Example 142 (General procedure (B))

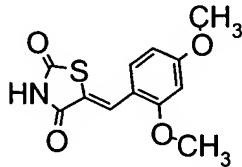
- 20 5-(2-Bromobenzylidene)thiazolidine-2,4-dione



¹H-NMR (DMSO-d₆): 7.33 (1H, t), 7.52 (1H, t), 7.60 (1H, d), 7.71 (1H, s), 7.77 (1H, d).

Example 143 (General procedure (B))

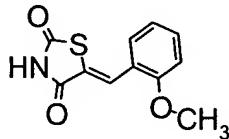
5-(2,4-Dimethoxybenzylidene)thiazolidine-2,4-dione



- 5 HPLC-MS (Method C): m/z: 266 (M+1) Rt = 4,40 min.

Example 144 (General procedure (B))

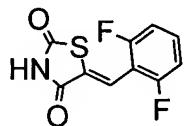
5-(2-Methoxybenzylidene)thiazolidine-2,4-dione



- 10 HPLC-MS (Method C): m/z: 236 (M+1); Rt = 4,17 min.

Example 145 (General procedure (B))

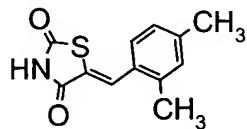
5-(2,6-Difluorobenzylidene)thiazolidine-2,4-dione



- 15 HPLC-MS (Method C): m/z: 242 (M+1); Rt = 4,30 min.

Example 146 (General procedure (B))

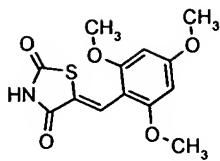
5-(2,4-Dimethylbenzylidene)thiazolidine-2,4-dione



- 20 HPLC-MS (Method C): m/z: 234 (M+1); Rt = 5,00 min.

Example 147 (General procedure (B))

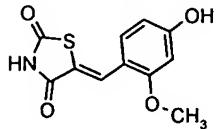
5-(2,4,6-Trimethoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 296 (M+1); Rt = 4,27 min.

Example 148 (General procedure (B))

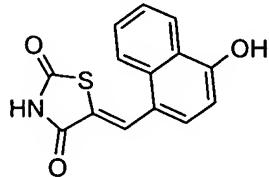
- 5 5-(4-Hydroxy-2-methoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 252 (M+1); Rt = 3,64 min.

Example 149 (General procedure (B))

- 10 5-(4-Hydroxynaphthalen-1-ylmethylene)thiazolidine-2,4-dione

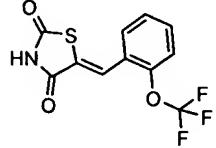


¹H-NMR (DMSO-d₆): δ = 7.04 (1H, d), 7.57 (2H, m), 7.67 (1H, t), 8.11 (1H, d), 8.25 (1H, d), 8.39 (1H, s) 11.1 (1H, s), 12.5 (1H, bs). HPLC-MS (Method C): m/z: 272 (M+1); Rt = 3.44 min.

15

Example 150 (General procedure (B))

- 5-(2-Trifluoromethoxybenzylidene)thiazolidine-2,4-dione

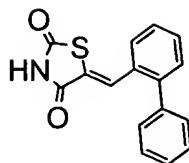


HPLC-MS (Method C): m/z: 290 (M+1); Rt = 4,94 min.

20

Example 151 (General procedure (B))

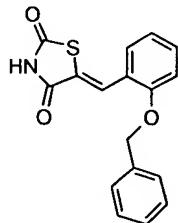
- 5-Biphenyl-2-ylmethylenethiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 282 (M+1); Rt = 5,17 min.

Example 152 (General procedure (B))

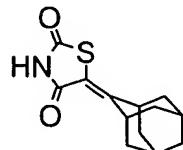
- 5 5-(2-Benzoyloxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 312 (M+1); Rt = 5,40 min.

Example 153 (General procedure (B))

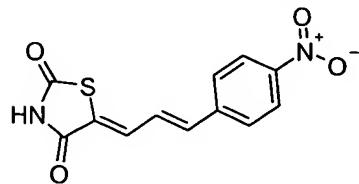
- 10 5-Adamantan-2-ylidenethiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 250 (M+1); Rt = 4,30 min.

Example 154 (General Procedure (B))

- 15 5-[3-(4-Nitrophenyl)allylidene]thiazolidine-2,4-dione

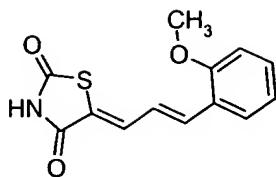


HPLC-MS (Method C): m/z: 277 (M+1); Rt = 3.63 min.

Example 155 (General Procedure (B))

- 20 5-[3-(2-Methoxyphenyl)allylidene]thiazolidine-2,4-dione

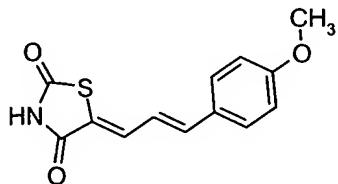
130



HPLC-MS (Method C): m/z: 262 (M+1); Rt = 3.81 min.

Example 156 (General Procedure (B))

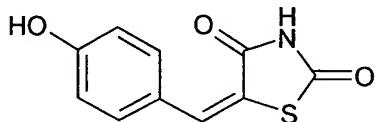
- 5 5-[3-(4-Methoxyphenyl)allylidene]thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 262 (M+1); Rt = 3.67 min.

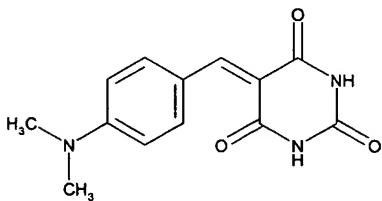
Example 157 (General procedure (B))

- 10 5-(4-Hydroxybenzylidene)thiazolidine-2,4-dione



Example 158 (General procedure (B))

- 5-(4-Dimethylaminobenzylidene)pyrimidine-2,4,6-trione

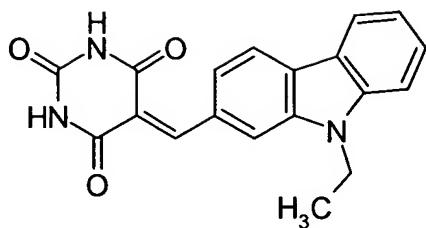


15

HPLC-MS (Method C): m/z = 260 (M+1) Rt = 2,16 min.

Example 159 (General procedure (B))

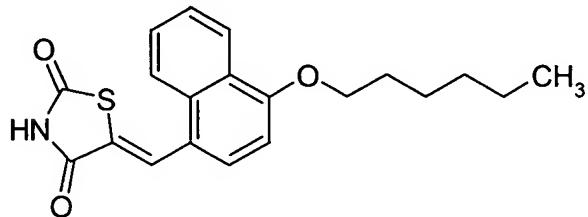
- 5-(9-Ethyl-9H-carbazol-2-ylmethylene)-pyrimidine-2,4,6-trione



HPLC-MS (Method C): m/z = 334 (M+1); Rt = 3.55 min.

Example 160 (General procedure (B))

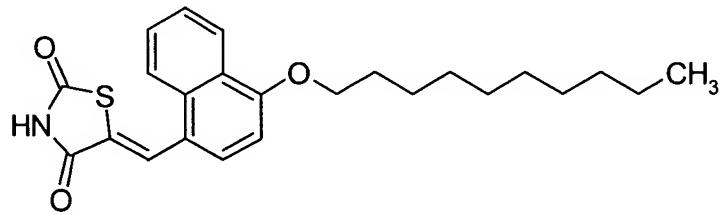
- 5 5-(4-Hexyloxy)naphthalen-1-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 356 (M+1); Rt = 5.75 min.

Example 161 (General procedure (B))

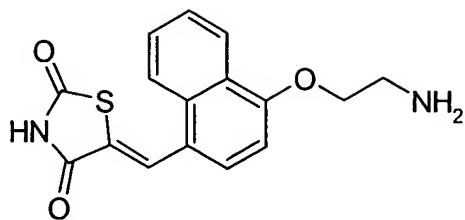
- 10 5-(4-Decyloxy)naphthalen-1-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 412 (M+1); Rt = 6.44 min.

Example 162 (General procedure (B))

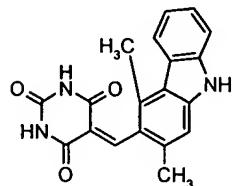
- 15 5-[4-(2-Aminoethoxy)-naphthalen-1-ylmethylene]-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 315 (M+1); Rt = 3.24 min.

Example 163 (General procedure (B))

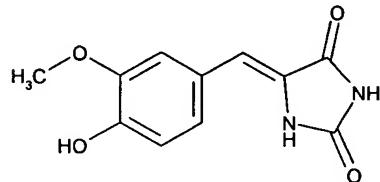
- 5 5-(2,4-Dimethyl-9H-carbazol-3-ylmethylene)-pyrimidine-2,4,6-trione



HPLC-MS (Method C): m/z = 334 (M+1); Rt = 3.14 min.

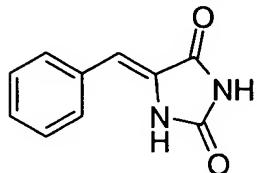
Example 164 (General procedure (B))

- 10 4-(4-Hydroxy-3-methoxybenzylidene)hydantoin



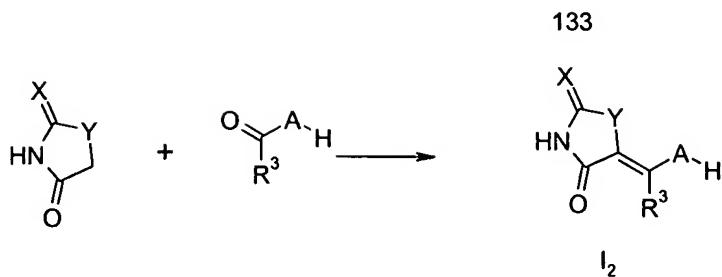
Example 165 (General procedure (B))

5-Benzylidenehydantoin



15

General procedure (C) for preparation of compounds of general formula I₂:

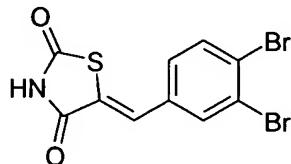


wherein X, Y, A, and R^3 are as defined above and A is optionally substituted with up to four substituents R^7 , R^8 , R^9 , and R^{10} as defined above.

- 5 This general procedure (C) is quite similar to general procedure (B) and is further illustrated in the following example:

Example 166 (General procedure (C))

5-(3,4-Dibromobenzylidene)thiazolidine-2,4-dione



A mixture of thiazolidine-2,4-dione (90%, 65 mg, 0.5 mmol), 3,4-dibromobenzaldehyde (132 mg, 0.5 mmol), and piperidine (247 μL , 2.5 mmol) was shaken in acetic acid (2 mL) at 110 °C for 16 hours. After cooling, the mixture was concentrated to dryness *in vacuo*.

- 15 The resulting crude product was shaken with water, centrifuged, and the supernatant was discarded. Subsequently the residue was shaken with ethanol, centrifuged, the supernatant was discarded and the residue was further evaporated to dryness to afford the title compound.

¹H NMR (Acetone- d_6): δ_H 7.99 (d, 1H), 7.90 (d, 1H), 7.70 (s, 1H), 7.54 (d, 1H); HPLC-MS

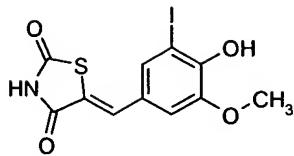
- 20 (Method A): m/z: 364 (M+1); Rt = 4.31 min.

The compounds in the following examples were similarly prepared. Optionally, the compounds can be further purified by filtration and washing with water instead of concentration *in vacuo*. Also optionally the compounds can be purified by washing with ethanol, water and/or heptane, or by preparative HPLC.

Example 167 (General procedure (C))

5-(4-Hydroxy-3-iodo-5-methoxybenzylidene)thiazolidine-2,4-dione

134

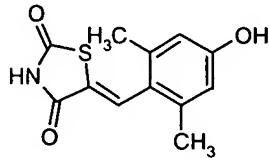


Mp = 256 °C; ^1H NMR (DMSO- d_6) δ = 12.5 (s,broad,1H), 10.5 (s,broad,1H), 7.69 (s,1H), 7.51 (d,1H), 7.19 (d,1H)3.88 (s,3H), ^{13}C NMR (DMSO- d_6) δ_{C} = 168.0, 167.7 , 149.0, 147.4, 133.0, 131.2, 126.7, 121.2, 113.5, 85.5, 56.5; HPLC-MS (Method A): m/z: 378 (M+1); Rt = 3.21 min.

5

Example 168 (General procedure (C))

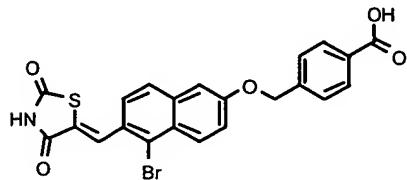
5-(4-Hydroxy-2,6-dimethylbenzylidene)thiazolidine-2,4-dione



10 HPLC-MS (Method C): m/z: 250 (M+1); Rt.= 2.45 min.

Example 169 (General procedure (C))

4-[5-Bromo-6-(2,4-dioxothiazolidin-5-ylidenemethyl)-naphthalen-2-yloxymethyl]-benzoic acid

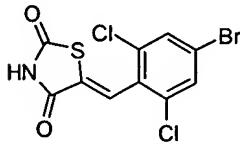


15

HPLC-MS (Method C): m/z: 506 (M+23); Rt.= 4.27 min.

Example 170 (General procedure (C))

5-(4-Bromo-2,6-dichlorobenzylidene)thiazolidine-2,4-dione

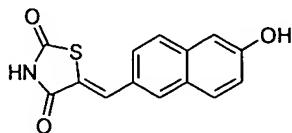


20

HPLC-MS (Method C): m/z: 354 (M+1); Rt.= 4.36 min.

Example 171 (General procedure (C))

5-(6-Hydroxy-2-naphthylmethylene) thiazolidine-2,4-dione



Mp 310-314 °C, ^1H NMR (DMSO- d_6): $\delta_{\text{H}} = 12.5$ (s,broad,1H), 8.06(d,1H), 7.90-

- 5 7.78(m,2H), 7.86 (s,1H), 7.58 (dd,1H), 7.20 7.12 (m,2H). ^{13}C NMR (DMSO- d_6): $\delta_{\text{C}} = 166.2$, 165.8 , 155.4, 133.3, 130.1, 129.1, 128.6, 125.4, 125.3, 125.1, 124.3, 120.0, 117.8, 106.8; HPLC-MS (Method A): m/z: 272 (M+1); Rt = 3.12 min.

Preparation of the starting material, 6-hydroxy-2-naphthalenecarbaldehyde:

10

6-Cyano-2-naphthalenecarbaldehyde (1.0 g, 5.9 mmol) was dissolved in dry hexane (15 mL) under nitrogen. The solution was cooled to -60 °C and a solution of diisobutyl aluminium hydride (DIBAH) (15 mL, 1M in hexane) was added dropwise. After the addition, the solution was left at room temperature overnight. Saturated ammonium chloride solution (20 mL) was added and the mixture was stirred at room temperature for 20 min, subsequently aqueous H_2SO_4 (10% solution, 15 mL) was added followed by water until all salt was dissolved. The resulting solution was extracted with ethyl acetate (3x), the combined organic phases were dried with MgSO_4 , evaporated to dryness to afford 0.89 g of 6-hydroxy-2-naphthalenecarbaldehyde.

20

Mp.: 153.5-156.5 °C; HPLC-MS (Method A): m/z: 173 (M+1); Rt = 2.67 min; ^1H NMR (DMSO- d_6): $\delta_{\text{H}} = 10.32$ (s,1H), 8.95 (d,1H), 10.02 (s,1H), 8.42 (s,broad,1H), 8.01 (d,1H), 7.82-7.78 (m,2H), 7.23-7.18 (m,2H).

25 Alternative preparation of 6-hydroxy-2-naphthalenecarbaldehyde:

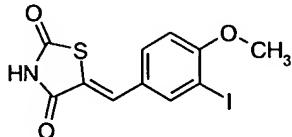
To a stirred cooled mixture of 6-bromo-2-hydroxynaphthalene (25.3 g, 0.113 mol) in THF (600 mL) at -78 °C was added n-BuLi (2.5 M, 100 mL, 0.250 mol) dropwise. The mixture turned yellow and the temperature rose to -64 °C. After ca 5 min a suspension appeared. After addition, the mixture was maintained at -78 °C. After 20 minutes, a solution of DMF (28.9 mL, 0.373 mol) in THF (100 mL) was added over 20 minutes. After addition, the mixture was allowed to warm slowly to room temperature. After 1 hour, the mixture was poured in ice/water (200 mL). To the mixture citric acid was added to a pH of 5. The mixture was stirred for 0.5 hour. Ethyl acetate (200 mL) was added and the organic layer was

separated and washed with brine (100 mL), dried over Na_2SO_4 and concentrated. To the residue was added heptane with 20% ethyl acetate (ca 50 mL) and the mixture was stirred for 1 hour. The mixture was filtered and the solid was washed with ethyl acetate and dried *in vacuo* to afford 16 g of the title compound.

5

Example 172 (General procedure (C))

5-(3-Iodo-4-methoxybenzylidene)thiazolidine-2,4-dione



¹H NMR (DMSO- d_6): δ_H 12.55 (s,broad,1H), 8.02 (d,1H), 7.72 (s,1H), 7.61 (d,1H), 7.18(d,1H),

10 3.88 (s,3H); ¹³C NMR (DMSO- d_6): δ_C 168.1, 167.7, 159.8, 141.5, 132.0, 130.8, 128.0, 122.1, 112.5, 87.5, 57.3. HPLC-MS (Method A): m/z: 362 (M+1); Rt = 4.08 min.

Preparation of the starting material, 3-iodo-4-methoxybenzaldehyde:

15 4-Methoxybenzaldehyde (0.5 g, 3.67 mmol) and silver trifluoroacetate (0.92 g, 4.19 mmol) were mixed in dichloromethane (25 mL). Iodine (1.19 g, 4.7 mmol) was added in small portions and the mixture was stirred overnight at room temperature under nitrogen. The mixture was subsequently filtered and the residue washed with DCM. The combined filtrates were treated with an aqueous sodium thiosulfate solution (1 M) until the colour disappeared.

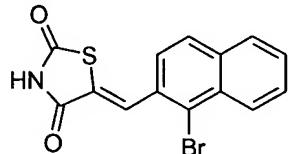
20 Subsequent extraction with dichloromethane (3 x 20 mL) followed by drying with MgSO_4 and evaporation *in vacuo* afforded 0.94 g of 3-iodo-4-methoxybenzaldehyde.

Mp 104-107 °C; HPLC-MS (Method A): m/z: 263 (M+1); Rt = 3.56 min.; ¹H NMR (CDCl_3): δ_H = 8.80 (s,1H), 8.31 (d,1H), 7.85 (dd,1H) 6.92 (d,1H), 3.99 (s, 3H).

25

Example 173 (General procedure (C))

5-(1-Bromonaphthalen-2-ylmethylene)thiazolidine-2,4-dione

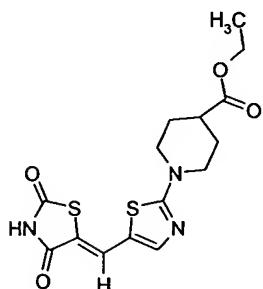


HPLC-MS (Method A): m/z: 336 (M+1); Rt = 4.46 min.

30

Example 174 (General procedure (C))

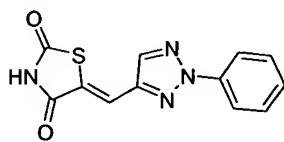
1-[5-(2,4-Dioxothiazolidin-5-ylidenemethyl)thiazol-2-yl]piperidine-4-carboxylic acid ethyl ester



- ¹H NMR (DMSO-*d*₆): δ_H = 7.88 (s,1H), 7.78 (s,1H), 4.10 (q,2H), 4.0-3.8 (m,2H), 3.40-3.18 (m,2H), 2.75-2.60 (m,1H), 2.04-1.88 (m,2H), 1.73-1.49 (m,2H), 1.08 (t,3H); HPLC-MS (Method A): m/z: 368 (M+1); Rt = 3.41 min.

Example 175 (General procedure (C))

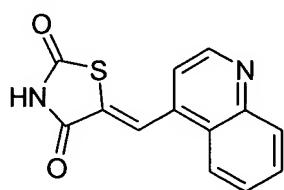
5-(2-Phenyl-[1,2,3]triazol-4-ylmethylene) thiazolidine-2,4-dione



- ¹H NMR (DMSO-*d*₆): δ_H = 12.6 (s,broad,1H), 8.46 (s,1H), 8.08 (dd,2H), 7.82 (s,1H), 7.70-7.45 (m, 3H). HPLC-MS (Method A): m/z: 273 (M+1); Rt = 3.76 min.

Example 176 (General procedure (C))

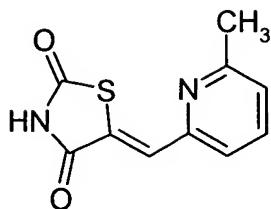
- 15 5-(Quinolin-4-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 257 (M+1); Rt = 2.40 min.

Example 177 (General procedure (C))

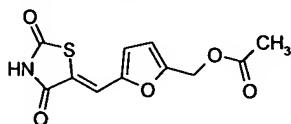
- 20 5-(6-Methylpyridin-2-ylmethylene)thiazolidine-2,4-dione



¹H NMR (DMSO-*d*₆): δ_H = 12.35 (s,broad,1H), 7.82 (t,1H), 7.78 (s,1H), 7.65 (d,1H), 7.18 (d,1H), 2.52 (s,3 H); HPLC-MS (Method A): m/z: 221 (M+1); Rt = 3.03 min.

5 Example 178 (General procedure (C))

5-(2,4-dioxothiazolidin-5-ylidenemethyl)-furan-2-ylmethylacetate

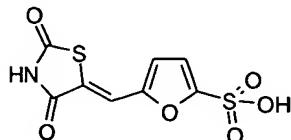


¹H NMR (DMSO-*d*₆): δ_H = 12.46 (s,broad,1H), 7.58 (s,1H), 7.05 (d,1H), 6.74 (s,1H), 5.13 (s,2H), 2.10 (s,3H). HPLC-MS (Method A): m/z: 208 (M-CH₃COO); Rt = 2.67 min.

10

Example 179 (General procedure (C))

5-(2,4-Dioxothiazolidin-5-ylidenemethyl)furan-2-sulfonic acid

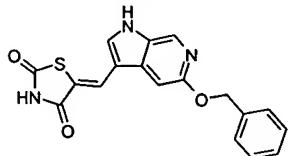


HPLC-MS (Method A): m/z: 276 (M+1); Rt = 0.98 min.

15

Example 180 (General procedure (C))

5-(5-Benzylxylo-1H-pyrrolo[2,3-c]pyridin-3-ylmethylene)-thiazolidine-2,4-dione

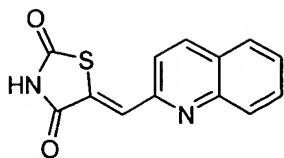


HPLC-MS (Method A): m/z: 352 (M+1); Rt = 3.01 min.

20

Example 181 (General procedure (C))

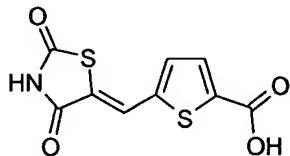
5-(Quinolin-2-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 257 (M+1); Rt = 3.40 min.

Example 182 (General procedure (C))

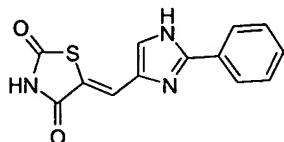
- 5 5-(2,4-Dioxothiazolidin-5-ylidenemethyl)thiophene-2-carboxylic acid



HPLC-MS (Method A): m/z: 256 (M+1); Rt = 1.96 min.

Example 183 (General procedure (C))

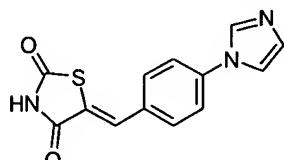
- 10 5-(2-Phenyl-1H-imidazol-4-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 272 (M+1); Rt = 2.89 min.

Example 184 (General procedure (C))

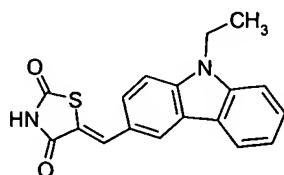
- 15 5-(4-Imidazol-1-yl-benzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 272 (M+1); Rt = 1.38 min.

Example 185 (General procedure (C))

- 20 5-(9-Ethyl-9H-carbazol-3-ylmethylene)thiazolidine-2,4-dione

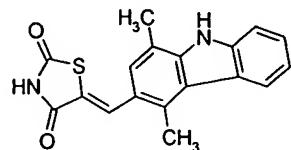


140

HPLC-MS (Method A): m/z: 323 (M+1); Rt = 4.52 min.

Example 186 (General procedure (C))

5-(1,4-Dimethyl-9H-carbazol-3-ylmethylene)thiazolidine-2,4-dione

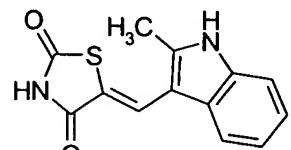


5

HPLC-MS (Method A): m/z: 323 (M+1); Rt = 4.35 min.

Example 187 (General procedure (C))

5-(2-Methyl-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



10

HPLC-MS (Method A): m/z: 259 (M+1); Rt = 3.24 min.

Example 188 (General procedure (C))

5-(2-Ethylindol-3-ylmethylene)thiazolidine-2,4-dione



15

2-Methylindole (1.0 g, 7.6mmol) dissolved in diethyl ether (100 mL) under nitrogen was treated with n-Butyl lithium (2 M in pentane, 22.8 mmol) and potassium *tert*-butoxide (15.2 mmol) with stirring at RT for 30 min. The temperature was lowered to -70 C and methyl iodide (15.2 mmol) was added and the resulting mixture was stirred at -70 for 2 h. Then 5 drops of water was added and the mixture allowed to warm up to RT. Subsequently, the mixture was poured into water (300 mL), pH was adjusted to 6 by means of 1N hydrochloric acid and the mixture was extracted with diethyl ether. The organic phase was dried with Na₂SO₄ and evaporated to dryness. The residue was purified by column chromatography on silica gel using heptane/ether(4/1) as eluent. This afforded 720 mg (69 %) of 2-ethylindole.

¹H NMR (DMSO-d₆): δ = 10.85 (1H,s); 7.39 (1H,d); 7.25 (1H,d); 6.98(1H,t); 6.90(1H,t); 6.10 (1H,s); 2.71 (2H,q); 1.28 (3H,t).

2-Ethylindole (0.5 g, 3.4mmol) dissolved in DMF (2 mL) was added to a cold (0 °C) premixed
5 (30 minutes) mixture of DMF (1.15 mL) and phosphorous oxychloride (0.64 g, 4.16 mmol). After addition of 2-ethylindole, the mixture was heated to 40 °C for 1 h, water (5 mL) was added and the pH adjusted to 5 by means of 1 N sodium hydroxide. The mixture was subsequently extracted with diethyl ether, the organic phase isolated, dried with MgSO₄ and evaporated to dryness affording 2-ethylindole-3-carbaldehyde (300 mg).

10

HPLC-MS (Method C): m/z:174 (M+1); Rt. =2.47 min.

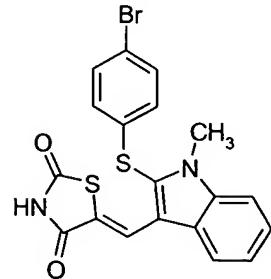
2-Ethylindole-3-carbaldehyde (170 mg) was treated with thiazolidine-2,4-dione using the general procedure (C) to afford the title compound (50 mg).

15

HPLC-MS (Method C):m/z: 273 (M+1); Rt.= 3.26 min.

Example 189 (General procedure (C))

5-[2-(4-Bromophenylsulfanyl)-1-methyl-1H-indol-3-ylmethylene]thiazolidine-2,4-dione

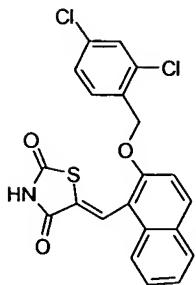


20

HPLC-MS (Method A): m/z: 447 (M+1); Rt = 5.25 min.

Example 190 (General procedure (C))

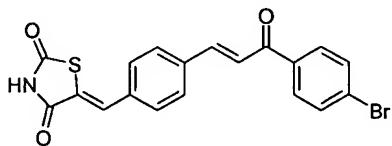
5-[2-(2,4-Dichlorobenzyl)oxy]-naphthalen-1-ylmethylene]thiazolidine-2,4-dione



HPLC-MS (Method A): (anyone 1) m/z: 430 (M+1); Rt = 5.47 min.

Example 191 (General procedure (C))

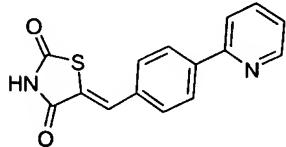
- 5 5-{4-[3-(4-Bromophenyl)-3-oxopropenyl]-benzylidene}thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 416 (M+1); Rt = 5.02 min.

Example 192 (General procedure (C))

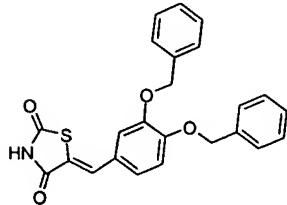
- 10 5-(4-Pyridin-2-ylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 283 (M+1), Rt = 2.97 min.

Example 193 (General procedure (C))

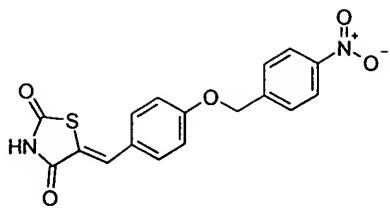
- 15 5-(3,4-Bisbenzyloxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 418 (M+1); Rt = 5.13 min.

Example 194 (General procedure (C))

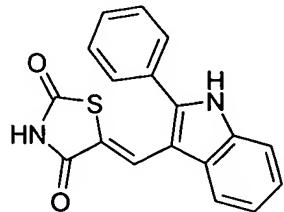
- 20 5-[4-(4-Nitrobenzyloxy)-benzylidene]thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 357 (M+1); Rt = 4.45 min.

Example 195 (General procedure (C))

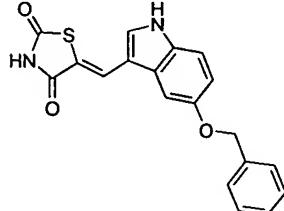
- 5 5-(2-Phenyl-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 321 (M+1); Rt = 3.93 min.

Example 196 (General procedure (C))

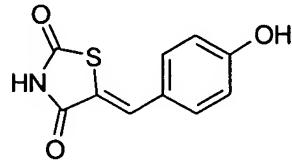
- 10 5-(5-Benzylxy-1H-indol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 351 (M+1); Rt = 4.18 min.

Example 197 (General procedure (C))

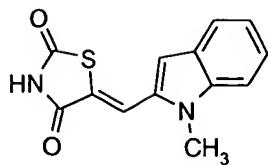
- 15 5-(4-Hydroxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 222 (M+1); Rt = 2.42 min.

Example 198 (General procedure (C))

- 5-(1-Methyl-1H-indol-2-ylmethylene)thiazolidine-2,4-dione



¹H NMR (DMSO-*d*₆): δ_H = 12.60 (s,broad,1H), 7.85 (s,1H), 7.68 (dd,1H), 7.55 (dd,1H), 7.38 (dt,1H), 7.11 (dt,1H) 6.84 (s,1H), 3.88 (s,3H); HPLC-MS (Method A): m/z: 259 (M+1); Rt = 4.00 min.

5

Example 199 (General procedure (C))

5-(5-Nitro-1H-indol-3-ylmethylene)thiazolidine-2,4-dione

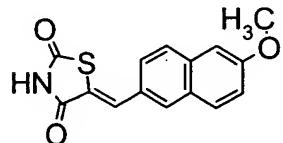


.Mp 330-333 °C, ¹H NMR (DMSO-*d*₆): δ_H = 12.62 (s,broad,1H), 8.95 (d,1H), 8.20 (s,1H), 8.12

10 (dd,1H), 7.98 (s,broad,1H), 7.68 (d,1H); HPLC-MS (Method A): m/z: 290 (M+1); Rt = 3.18 min.

Example 200 (General procedure (C))

5-(6-Methoxynaphthalen-2-ylmethylene)thiazolidine-2,4-dione

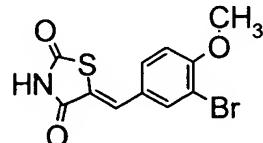


15

HPLC-MS (Method A): m/z: 286 (M+1); Rt = 4.27 min.

Example 201 (General procedure (C))

5-(3-Bromo-4-methoxybenzylidene)thiazolidine-2,4-dione

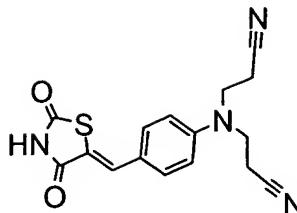


20

HPLC-MS (Method A): m/z: 314 (M+1), Rt = 3.96 min.

Example 202 (General procedure (C))

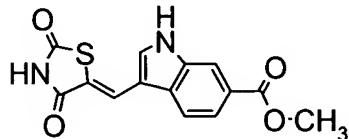
3-{(2-Cyanoethyl)-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenyl]amino}propionitrile



HPLC-MS (Method A): m/z: 327 (M+1); Rt = 2.90 min.

Example 203 (General procedure (C))

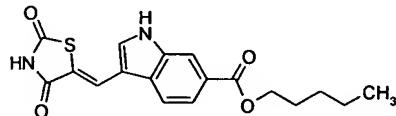
- 5 3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-6-carboxylic acid methyl ester



HPLC-MS (Method A): m/z: 303 (M+1); Rt = 3.22-3-90 min.

Example 204

- 10 3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-6-carboxylic acid pentyl ester.



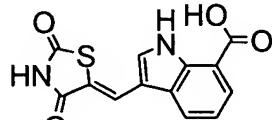
3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-6-carboxylic acid methyl ester (example 203, 59 mg; 0.195mmol) was stirred in pentanol (20 mL) at 145 °C for 16 hours. The mixture was evaporated to dryness affording the title compound (69 mg).

15

HPLC-MS (Method C): m/z: 359 (M+1); Rt.= 4.25 min.

Example 205 (General procedure (C))

3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-7-carboxylic acid

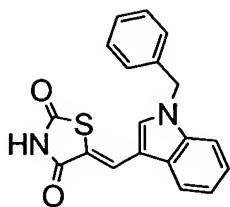


20

HPLC-MS (Method A): m/z: 289 (M+1); Rt = 2.67 min.

Example 206 (General procedure (C))

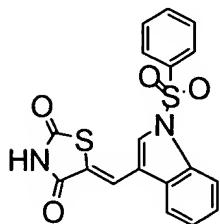
5-(1-Benzylindol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 335 (M+1); Rt = 4.55 min.

Example 207 (General procedure (C))

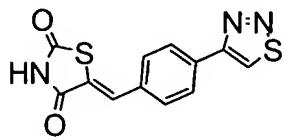
- 5 5-(1-Benzenesulfonylindol-3-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: = 385 (M+1); Rt = 4.59 min.

Example 208 (General procedure (C))

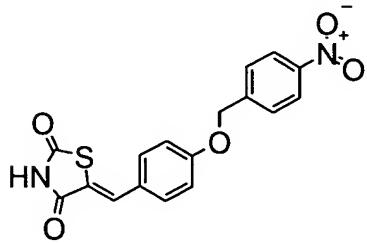
- 10 5-(4-[1,2,3]Thiadiazol-4-ylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 290 (M+1); Rt = 3.45 min.

Example 209 (General procedure (C))

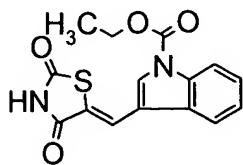
- 15 5-[4-(4-Nitrobenzyloxy)-benzylidene]thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 357 (M+1); Rt = 4.42 min.

Example 210 (General procedure (C))

3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-1-carboxylic acid ethyl ester

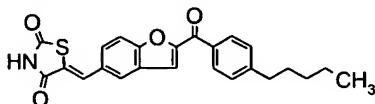


HPLC-MS (Method A): m/z: 317 (M+1); Rt = 4.35 min.

5

Example 211 (General procedure (C))

5-[2-(4-Pentylbenzoyl)-benzfuran-5-ylmethylene]thiazolidine-2,4-dione

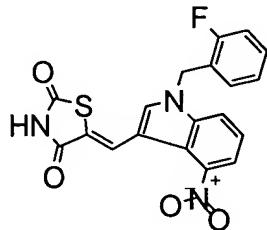


HPLC-MS (Method A): m/z: 420 (M+1); Rt = 5.92 min.

10

Example 212 (General procedure (C))

5-[1-(2-Fluorobenzyl)-4-nitroindol-3-ylmethylene]thiazolidine-2,4-dione

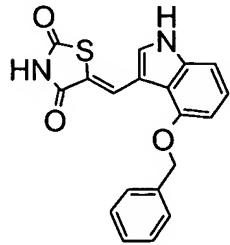


HPLC-MS (Method A): (Anyone 1) m/z: 398 (M+1); Rt = 4.42 min.

15

Example 213 (General procedure (C))

5-(4-Benzylxyloxyindol-3-ylmethylene)thiazolidine-2,4-dione

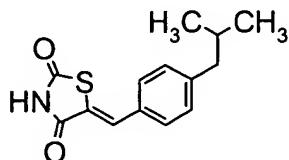


HPLC-MS (Method A): m/z: 351 (M+1); Rt = 3.95 min.

20

Example 214 (General procedure (C))

5-(4-Isobutylbenzylidene)-thiazolidine-2,4-dione

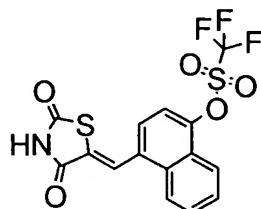


HPLC-MS (Method A): m/z: 262 (M+1); Rt = 4.97 min.

5

Example 215 (General procedure (C))

Trifluoromethanesulfonic acid 4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yl ester



HPLC-MS (Method A): m/z: 404 (M+1); Rt = 4.96 min.

10

Preparation of starting material:

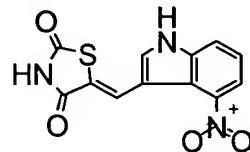
4-Hydroxy-1-naphthaldehyde (10 g, 58 mmol) was dissolved in pyridin (50 ml) and the mixture was cooled to 0-5 °C. With stirring, trifluoromethanesulfonic acid anhydride (11.7 ml, 70 mmol) was added drop-wise. After addition was complete, the mixture was allowed to

15 warm up to room temperature, and diethyl ether (200 ml) was added. The mixture was washed with water (2 x 250 ml), hydrochloric acid (3N, 200 ml), and saturated aqueous sodium chloride (100 ml). After drying (MgSO4), filtration and concentration in vacuo, the residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:4). This afforded 8.35 g (47%) trifluoromethanesulfonic acid 4-

20 formylnaphthalen-1-yl ester, mp 44-46.6 °C.

Example 216 (General procedure (C))

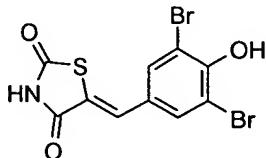
5-(4-Nitroindol-3-ylmethylene)-thiazolidine-2,4-dione



25 HPLC-MS (Method A): m/z: 290 (M+1); Rt = 3.14 min.

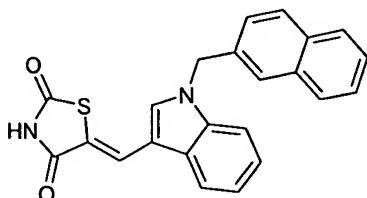
Example 217 (General procedure (C))

5-(3,5-Dibromo-4-hydroxy-benzylidene)thiazolidine-2,4-dione



- 5 ¹H NMR (DMSO-d₆): δ_H = 12.65 (broad, 1H), 10.85 (broad, 1H), 7.78 (s, 2H), 7.70 (s, 1H); HPLC-MS (Method A): m/z: 380 (M+1); Rt = 3.56 min.

Example 218 (General procedure (C))



- 10 HPLC-MS (Method A): m/z: 385 (M+1); Rt = 5.08 min.

General procedure for preparation of starting materials for examples 218 - 221:

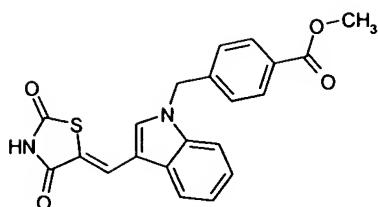
Indole-3-carbaldehyde (3.8 g, 26 mmol) was stirred with potassium hydroxide (1.7 g) in acetone (200 mL) at RT until a solution was obtained indicating full conversion to the indole 15 potassium salt. Subsequently the solution was evaporated to dryness *in vacuo*. The residue was dissolved in acetone to give a solution containing 2.6 mmol/20 mL.

20 20 mL portions of this solution were mixed with equimolar amounts of arylmethyli bromides in acetone (10 mL). The mixtures were stirred at RT for 4 days and subsequently evaporated to dryness and checked by HPLC-MS. The crude products, 1-benzylated indole-3-carbaldehydes, were used for the reaction with thiazolidine-2,4-dione using the general procedure C.

Example 219 (General procedure (C))

- 25 4-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indol-1-ylmethyl]benzoic acid methyl ester

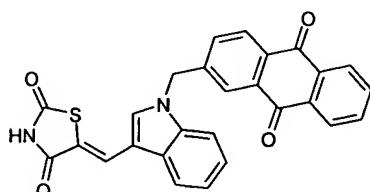
150



HPLC-MS (Method A): m/z: 393 (M+1); Rt = 4.60 min.

Example 220 (General procedure (C))

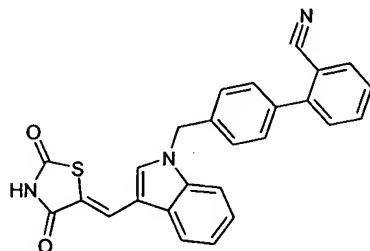
- 5 5-[1-(9,10-Dioxo-9,10-dihydroanthracen-2-ylmethyl)-1H-indol-3-ylmethylene]thiazolidine-2,4-dione



HPLC-MS (Method A): m/z: 465 (M+1); Rt = 5.02 min.

10 Example 221 (General procedure (C))

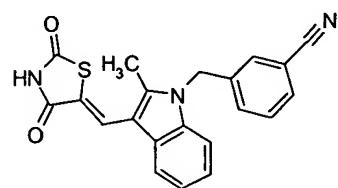
- 4'-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indol-1-ylmethyl]biphenyl-2-carbonitrile



HPLC-MS (Method A): m/z: 458 (M+23); Rt = 4.81 min.

15 Example 222 (General procedure (C))

- 3-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)-2-methylindol-1-ylmethyl]benzonitrile.



2-Methylindole-3-carbaldehyde (200 mg, 1.26 mmol) was added to a slurry of 3-bromomethylbenzenecarbonitrile (1.26 mmol) followed by sodium hydride, 60%, (1.26 mmol) in DMF (2 mL). The mixture was shaken for 16 hours, evaporated to dryness and washed

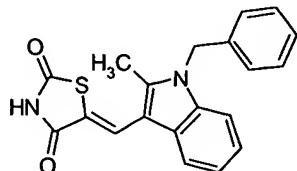
with water and ethanol. The residue was treated with thiazolidine-2,4-dione following the general procedure C to afford the title compound (100 mg).

HPLC-MS (Method C): m/z: 374 (M+1); Rt. = 3.95 min.

5

Example 223 (General procedure (C))

5-(1-Benzyl-2-methylindol-3-ylmethylene)thiazolidine-2,4-dione.

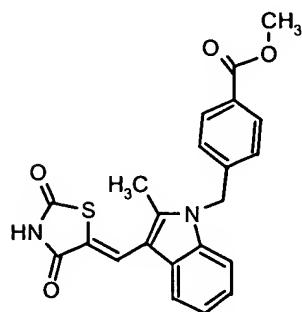


This compound was prepared in analogy with the compound described in example 222 from
10 benzyl bromide and 2-methylindole-3-carbaldehyde, followed by reaction with thiazolidine-
2,4-dione resulting in 50 mg of the title compound.

HPLC-MS (Method C): m/z: 349 (M+1); Rt. = 4.19 min.

15 Example 224

4-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)-2-methylindol-1-ylmethyl]benzoic acid methyl ester



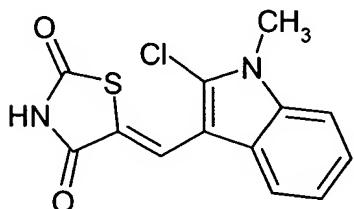
This compound was prepared in analogy with the compound described in example 222 from
20 4-(bromomethyl)benzoic acid methyl ester and 2-methylindole-3-carbaldehyde, followed by
reaction with thiazolidine-2,4-dione.

HPLC-MS (Method C): m/z: 407 (M+1); Rt.= 4.19 min.

152

Example 225 (General procedure (C))

5-(2-Chloro-1-methyl-1H-indol-3-ylmethylene)thiazolidine-2,4-dione

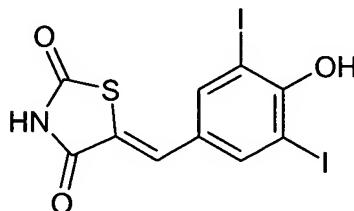


HPLC-MS (Method A): m/z: 293 (M+1); Rt = 4.10 min.

5

Example 226 (General procedure (C))

5-(4-Hydroxy-3,5-diiodo-benzylidene)-thiazolidine-2,4-dione

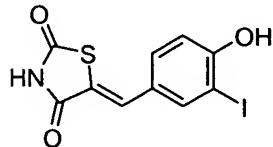


HPLC-MS (Method A): m/z: 474 (M+1); Rt = 6.61 min.

10

Example 227 (General procedure (C))

5-(4-Hydroxy-3-iodobenzylidene)thiazolidine-2,4-dione



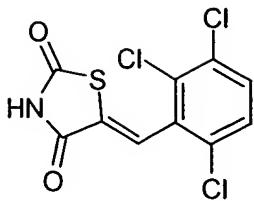
HPLC-MS (Method C): m/z: 348 (M+1); Rt. = 3.13 min

15 $^1\text{H-NMR}$: (DMSO- d_6): 11.5 (1H,broad); 7.95(1H,d); 7.65(1H,s); 7.45 (1H,dd); 7.01(1H,dd); 3.4 (1H,broad).

Example 228 (General procedure (C))

20 5-(2,3,6-Trichlorobenzylidene)thiazolidine-2,4-dione

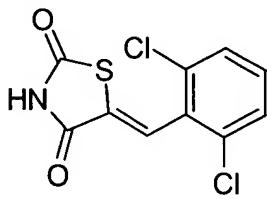
153



H PLC-MS (Method C): m/z: 309 (M+1); Rt.= 4.07 min

5 Example 229 (General procedure (C))

5-(2,6-Dichlorobenzylidene)thiazolidine-2,4-dione



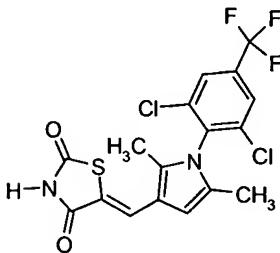
Mp. 152-154°C.

HPLC-MS (Method C): m/z: 274 (M+1), Rt.= 3.70 min

10 $^1\text{H-NMR}$: (DMSO- d_6): 12.8 (1H, broad); 7.72 (1H,s); 7.60 (2H,d); 7.50 (1H,t).

Example 230 (General procedure (C))

5-[1-(2,6-Dichloro-4-trifluoromethylphenyl)-2,5-dimethyl-1*H*-pyrrol-3-ylmethylene]thiazolidine-2,4-dione



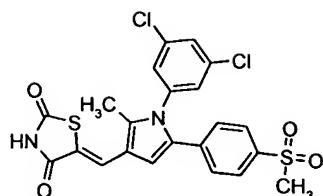
15

HPLC-MS (Method C): m/z: 436 (M+1); Rt. 4.81 min

Example 231 (General procedure (C))

5-[1-(3,5-Dichlorophenyl)-5-(4-methanesulfonylphenyl)-2-methyl-1*H*-pyrrol-3-ylmethylene]-20 thiazolidine-2,4-dione

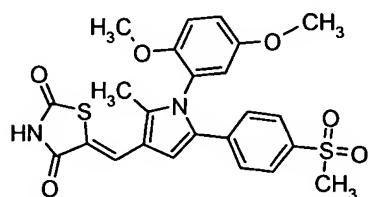
154



HPLC-MS (Method C): m/z: 508 (M+1); Rt. = 4.31 min

Example 232 (General procedure (C))

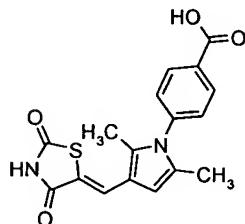
- 5 5-[1-(2,5-Dimethoxyphenyl)-5-(4-methanesulfonylphenyl)-2-methyl-1*H*-pyrrol-3-ylmethylene]-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 499 (M+1); Rt. = 3.70 min

- 10 Example 233 (General procedure (C))

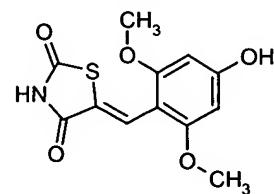
4-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)-2,5-dimethylpyrrol-1-yl]benzoic acid



HPLC-MS (Method C): m/z: 342 (M+1); Rt. = 3.19 min

- 15 Example 234 (General procedure (C))

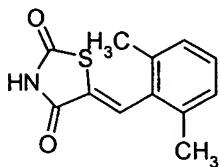
5-(4-Hydroxy-2,6-dimethoxybenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 282 (M+1); Rt. = 2.56, mp=331-333 °C

Example 235 (General procedure (C))

5-(2,6-Dimethylbenzylidene)thiazolidine-2,4-dione

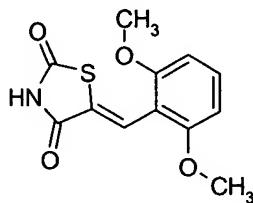


M.p: 104-105 °C

- 5 HPLC-MS (Method C): m/z: 234 (M+1); Rt.= 3.58 min,

Example 236 (General procedure (C))

5-(2,6-Dimethoxybenzylidene)thiazolidine-2,4-dione

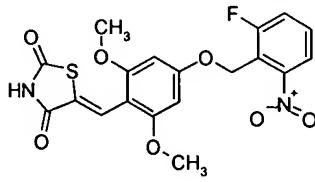


10 Mp: 241-242 °C

- HPLC-MS (Method C): m/z: 266 (M+1); Rt.= 3.25 min;

Example 237 (General procedure (C))

5-[4-(2-Fluoro-6-nitrobenzyloxy)-2,6-dimethoxybenzylidene]thiazolidine-2,4-dione



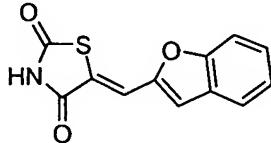
15

Mp: 255-256 °C

- HPLC-MS (Method C): m/z: 435 (M+1), Rt 4.13 min,

Example 238 (General procedure (C))

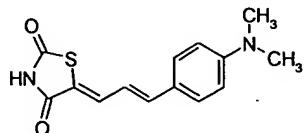
- 20 5-Benzofuran-2-ylmethylenethiazolidine-2,4-dione



- HPLC-MS (Method C): m/z: 246 (M+1); Rt.= 3.65 min, mp = 265-266 °C .

Example 239 (General procedure (C))

5-[3-(4-Dimethylaminophenyl)allylidene]thiazolidine-2,4-dione

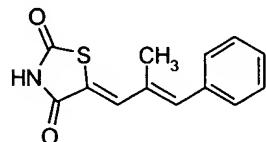


5 HPLC-MS (Method C): m/z:276(M+1); Rt.= 3.63, mp = 259-263 °C

 $^1\text{H-NMR}$: (DMSO- d_6) δ = 12.3 (1H,broad); 7.46 (2H,d); 7.39 (1H,d); 7.11 (1H,d); 6.69 (2H,d); 6.59 (1H, dd); 2.98 (3H,s).

Example 240 (General procedure (C))

10 5-(2-Methyl-3-phenylallylidene)thiazolidine-2,4-dione

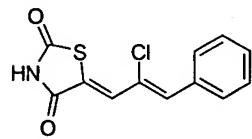


Mp: 203-210 °C

HPLC-MS (Method C): m/z: 246 (M+1); Rt = 3.79 min.

15 Example 241 (General procedure (C))

5-(2-Chloro-3-phenylallylidene)thiazolidine-2,4-dione



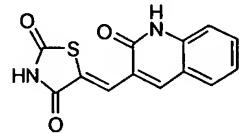
Mp: 251-254 °C

HPLC-MS (Method C): m/z: 266 (M+1; Rt = 3.90 min

20

Example 242 (General procedure (C))

5-(2-Oxo-1,2-dihydroquinolin-3-ylmethylene)thiazolidine-2,4-dione

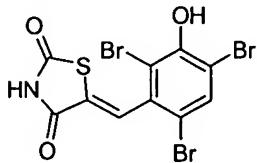


25 Mp: 338-347 °C

HPLC-MS (Method C): m/z: 273 (M+1); Rt. = 2.59 min.

Example 243 (General procedure (C))

5-(2,4,6-Tribromo-3-hydroxybenzylidene)thiazolidine-2,4-dione.



5

HPLC-MS (Method C): m/z: 459 (M+1); Rt.= 3.65 min.

Example 244 (General procedure (C))

5-(5-Bromo-2-methylindol-3-ylmethylene)thiazolidine-2,4-dione.

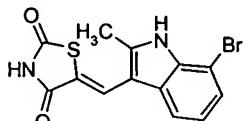


10

HPLC-MS (Method C): m/z: 339 (M+1); Rt = 3.37min.

Example 245 (General procedure (C))

5-(7-Bromo-2-methylindol-3-ylmethylene)thiazolidine-2,4-dione.

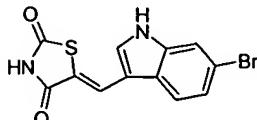


15

HPLC-MS (Method C): m/z: 319 (M+1); Rt = 3.48min.

Example 246 (General procedure (C))

5-(6-Bromoindol-3-ylmethylene)thiazolidine-2,4-dione.

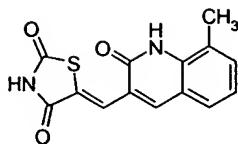


20

HPLC-MS (Method C): m/z: 325 (M+1); Rt = 3.54 min.

Example 247 (General procedure (C))

5-(8-Methyl-2-oxo-1,2-dihydroquinolin-3-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 287 (M+1); Rt = 2.86 min.

5 Example 248 (General procedure (C))

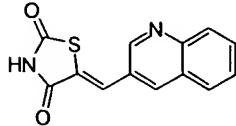
5-(6-Methoxy-2-oxo-1,2-dihydroquinolin-3-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 303 (M+1); Rt = 2.65 min.

10 Example 249 (General procedure (C))

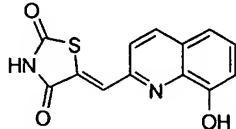
5-Quinolin-3-ylmethylenethiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 257 (M+1); Rt = 2.77 min.

15 Example 250 (General procedure (C))

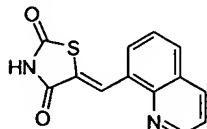
5-(8-Hydroxyquinolin-2-ylmethylene)thiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 273 (M+1); Rt = 3.44 min.

20 Example 251 (General procedure (C))

5-Quinolin-8-ylmethylenethiazolidine-2,4-dione.



HPLC-MS (Method C): m/z: 257 (M+1); Rt = 3.15 min.

Example 252 (General procedure (C))

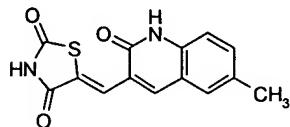
5-(1-Bromo-6-methoxynaphthalen-2-ylmethylene)thiazolidine-2,4-dione.



- 5 HPLC-MS (Method C): m/z: 366 (M+1); Rt = 4.44 min.

Example 253 (General procedure (C))

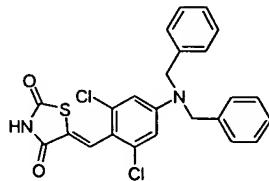
5-(6-Methyl-2-oxo-1,2-dihydroquinolin-3-ylmethylene)thiazolidine-2,4-dione.



- 10 HPLC-MS (Method C): m/z: 287 (M+1); Rt. = 2.89 min.

Example 254 (General procedure (D))

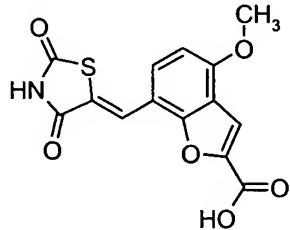
5-(2,6-Dichloro-4-dibenzylaminobenzylidene)thiazolidine-2,4-dione.



- 15 HPLC-MS (Method C): m/z: 469 (M+1); Rt = 5.35 min.

Example 255 (General Procedure (C))

7-(2,4-Dioxothiazolidin-5-ylidenemethyl)-4-methoxybenzofuran-2-carboxylic acid



- 20 HPLC-MS (Method C): m/z: 320 (M+1); Rt = 2.71 min.

Preparation of the intermediate, 7-formyl-4-methoxybenzofuran-2-carboxylic acid:

A mixture of 2-hydroxy-6-methoxybenzaldehyde (6.4 g, 42 mmol), ethyl bromoacetate (14.2 mL, 128 mmol) and potassium carbonate (26 g, 185 mmol) was heated to 130 °C. After 3 h the mixture was cooled to room temperature and acetone (100 mL) was added, the mixture was subsequently filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:4). This afforded 7.5 g (55%) of ethyl 4-methoxybenzofuran-2-carboxylate.

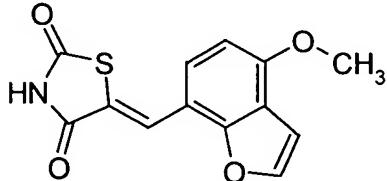
A solution of ethyl 4-methoxybenzofuran-2-carboxylate (6.9 g, 31.3 mmol) in dichloromethane (70 ml) was cooled to 0 °C and a solution of titanium tetrachloride (13.08 g, 10 69 mmol) was added drop wise. After 10 minutes dichloromethoxymethane (3.958 g, 34 mmol) was added over 10 minutes. After addition, the mixture was warmed to room temperature for 18 hours and the mixture poured into hydrochloric acid (2N, 100 mL). The mixture was stirred for 0.5 hour and then extracted with a mixture of ethyl acetate and toluene (1:1). The organic phase was dried over Na₂SO₄ and concentrated *in vacuo*. The 15 residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:4). This afforded 5.8 g (80%) of ethyl 7-formyl-4-methoxybenzofuran-2-carboxylate.

7-formyl-4-methoxybenzofuran-2-carboxylate (5.0 g, 21.5 mmol) and sodium carbonate (43 20 mmol) in water (100 mL) was refluxed until a clear solution appeared (about 0.5 hour). The solution was filtered and acidified to pH = 1 with hydrochloric acid (2 N), the resulting product was filtered off and washed with ethyl acetate and ethanol and dried to afford 3.5 g (74%) of 7-formyl-4-methoxybenzofuran-2-carboxylic acid as a solid.

25 ¹H NMR (DMSO-d₆): δ = 10.20 (s, 1H) ; 8.07 (d, 1H) ; 7.70 (s, 1H) ; 7.17 (d, 1H) ; 4.08 (s, 3H).

Example 256 (General Procedure (C))

5-(4-Methoxybenzofuran-7-ylmethylene)thiazolidine-2,4-dione



30

HPLC-MS (Method C): m/z: 267 (M+1); Rt = 3.30 min.

Preparation of the intermediate, 4-methoxybenzofuran-7-carbaldehyde:

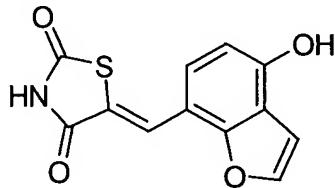
A mixture of 7-formyl-4-methoxybenzofuran-2-carboxylic acid (3.0 g, 13.6 mmol) and Cu (0.6 g, 9.44 mmol) in quinoline (6 mL) was refluxed. After 0.5 h the mixture was cooled to room temperature and water (100 mL) and hydrochloric acid (10 N, 20 mL) were added. The mixture was extracted with a mixture of ethyl acetate and toluene (1:1), filtered through celite and the organic layer separated and washed with a sodium carbonate solution, dried over Na₂SO₄ and concentrated *in vacuo* to afford 1.5 g crude product. Column chromatography 10 SiO₂, EtOAc/heptanes=1/4 gave 1.1 g (46%) of 4-methoxybenzofuran-7-carbaldehyde as a solid.

¹H NMR (CDCl₃): δ: 10.30 (s,1H) ; 7.85 (d,1H) ; 7.75 (d,1H) ; 6.98 (d,1H) ; 6.87 (d,1H) ; 4.10 (s,3H). HPLC-MS (Method C) :m/z: 177 (M+1); Rt. = 7.65 min.

15

Example 257 (General Procedure (C))

5-(4-Hydroxybenzofuran-7-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: = 262 (M+1); Rt 2.45 min.

20

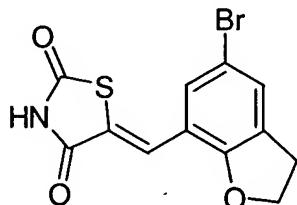
Preparation of the intermediate, 4-hydroxybenzofuran-7-carbaldehyde

A mixture of 4-methoxybenzofuran-7-carbaldehyde (1.6 g, 9.1 mmol) and pyridine hydrochloride (4.8 g, 41.7mmol) in quinoline (8 mL) was refluxed. After 8 h the mixture was 25 cooled to room temperature and poured into water (100 mL) and hydrochloric acid (2 N) was added to pH = 2. The mixture was extracted with a mixture of ethyl acetate and toluene (1:1), washed with a sodium carbonate solution, dried with Na₂SO₄ and concentrated *in vacuo* to afford 0.8 g crude product. This was purified by column chromatography on silica gel, eluting with a mixture of ethyl acetate and heptane (1:3). This afforded 250 mg of 4- 30 hydroxybenzofuran-7-carbaldehyde as a solid.

¹H NMR (DMSO-d₆): δ = 11.35 (s, broad, 1H); 10.15 (s, 1H); 8.05 (d, 1H); 7.75 (d, 1H); 7.10 (d, 1H); 6.83 (d, 1H). HPLC-MS (Method C): m/z: 163 (M+1); Rt. = 6.36 min.

Example 258 (General Procedure (C))

- 5 5-(5-Bromo-2,3-dihydrobenzofuran-7-ylmethylene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 328 (M+1); Rt = 3.66 min.

Preparation of the intermediate, 5-bromo-2,3-dihydrobenzofuran-7-carbaldehyde:

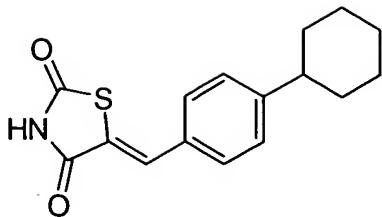
- 10 To a cooled (15 °C) stirred mixture dihydrobenzofuran (50.9 g, 0.424 mol) in acetic acid (500 mL), a solution of bromine (65.5 mL, 1.27 mol) in acetic acid (200 mL) was added drop wise over 1 hour. After stirring for 18 hours, a mixture of Na₂S₂O₅ (150 g) in water (250 mL) was added carefully, and the mixture was concentrated *in vacuo*. Water (200 mL) was added and the mixture was extracted with ethyl acetate containing 10% heptane, dried over Na₂SO₄ and 15 concentrated *in vacuo* to give crude 5,7-dibromo-2,3-dihydrobenzofuran which was used as such for the following reaction steps. To a cooled solution (-78 °C) of crude 5,7-dibromo-2,3-dihydrobenzofuran (50.7 g, 0.182 mol) in THF (375 mL) a solution of n-BuLi (2.5 M, 80 mL, 0.200 mol) in hexane was added. After addition, the mixture was stirred for 20 min. DMF (16 mL) was then added drop wise at -78 °C. After addition, the mixture was stirred at room 20 temperature for 3 h and then the mixture was poured into a mixture of ice water, (500 mL) and hydrochloric acid (10 N, 40 mL) and extracted with toluene, dried over Na₂SO₄ and concentrated *in vacuo*. Column chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:4) afforded 23 g of 5-bromo-2,3-dihydrobenzofuran-7-carbaldehyde as a solid.

25

¹H NMR (CDCl₃): δ: 10.18 (s, 1H); 7.75 (d, 1H); 7.55 (d, 1H); 4.80 (t, 2H); 3.28 (t, 2H).

Example 259 (General Procedure (C))

- 5-(4-Cyclohexylbenzylidene)thiazolidine-2,4-dione



HPLC-MS (Method C): m/z: 288 (M+1); Rt = 5.03 min.

Preparation of the intermediate, 4-cyclohexylbenzaldehyde:

5

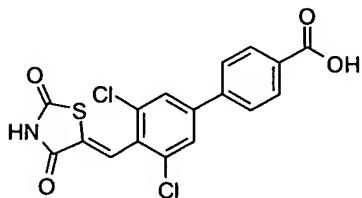
This compound was synthesized according to a modified literature procedure (*J. Org. Chem.*, **37**, No.24, (1972), 3972-3973).

Cyclohexylbenzene (112.5 g, 0.702 mol) and hexamethylenetetramine (99.3 g, 0.708 mol) were mixed in TFA (375 mL). The mixture was stirred under nitrogen at 90 °C for 3 days.

- 10 After cooling to room temperature the red-brown mixture was poured into ice-water (3600 ml) and stirred for 1 hour. The solution was neutralized with Na₂CO₃ (2 M solution in water) and extracted with dichloromethane (2.5 L). The organic phase was dried (Na₂SO₄) and the solvent was removed *in vacuo*. The remaining red-brown oil was purified by fractional distillation to afford the title compound (51 g, 39%).
- 15 ¹H NMR (CDCl₃): δ 9.96 (s, 1H), 7.80 (d, 2H), 7.35 (d, 2H), 2.58 (m, 1H), 1.94-1.70 (m, 5 H), 1.51-1.17 (m, 5H)

Other ligands of the invention include

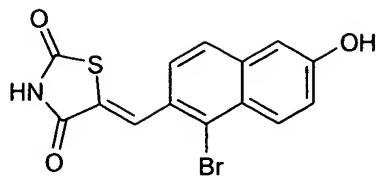
- 20 3',5'-Dichloro-4'-(2,4-dioxothiazolidin-5-ylidenemethyl)biphenyl-4-carboxylic acid:



Example 260 (General procedure (C))

5-(1-Bromo-6-hydroxynaphthalen-2-ylmethylene)-thiazolidine-2,4-dione

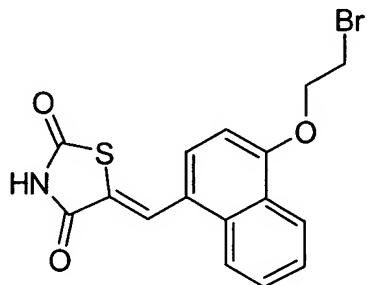
164



HPLC-MS (Method C): m/z = 350 (M+1); Rt. = 3.45 min.

Example 261 (General procedure (C))

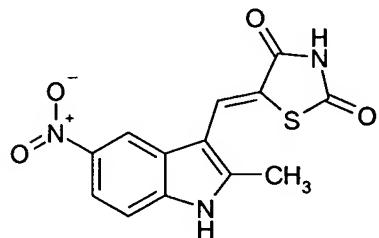
- 5 5-[4-(2-Bromoethoxy)-naphthalen-1-ylmethylene]-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 380 (M+1); Rt = 3.52 min.

Example 262 (General procedure (C))

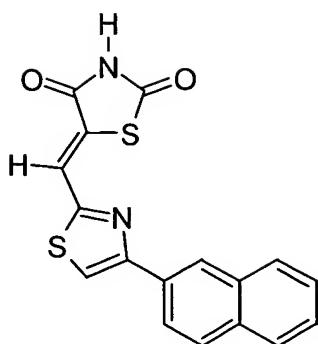
- 10 5-(2-Methyl-5-nitro-1H-indol-3-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 304 (M+1); Rt = 2.95 min.

Example 263 (General procedure (C))

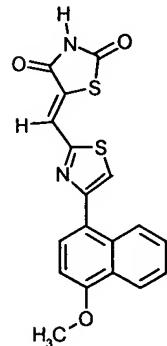
- 15 5-(4-Naphthalen-2-yl-thiazol-2-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 339 (M+1); Rt.= 4.498 min.

Example 264 (General procedure (C))

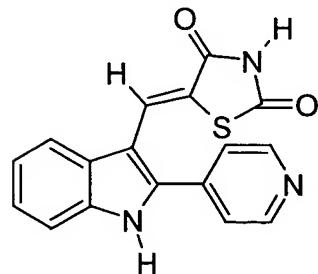
- 5 5-[4-(4-Methoxy-naphthalen-1-yl)-thiazol-2-ylmethylene]-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 369 (M+1); Rt.= 4.456 min.

Example 265 (General procedure (C))

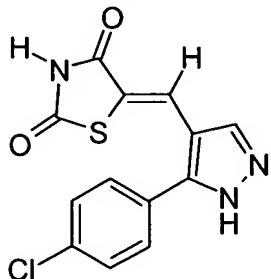
- 10 5-(2-Pyridin-4-yl-1H-indol-3-ylmethylene)-thiazolidine-2,4-dione



HPLC-MS (Method C): m/z = 322 (M+1); Rt. = 2.307 min.

Example 266 (General procedure (C))

5-[5-(4-Chlorophenyl)-1H-pyrazol-4-ylmethylene]-thiazolidine-2,4-dione

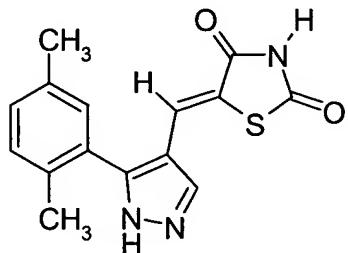


HPLC-MS (Method C): m/z = 306 (M+1); Rt.= 3.60 min.

5

Example 267 (General procedure (C))

5-[5-(2,5-Dimethylphenyl)-1H-pyrazol-4-ylmethylene]-thiazolidine-2,4-dione

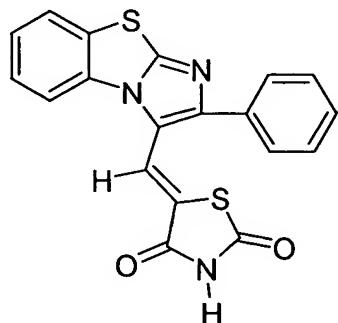


HPLC-MS (Method C): m/z = 300 (M+1); Rt. = 3.063 min.

10

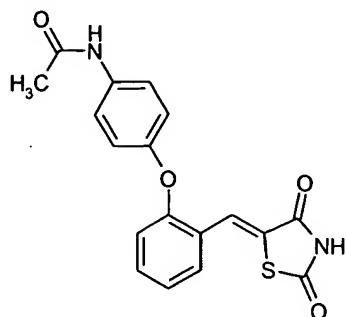
Example 268 (General procedure (C))

5-(2-Phenyl-benzo[d]imidazo[2,1-b]thiazol-3-ylmethylene)-thiazolidine-2,4-dione



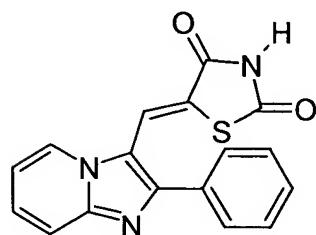
HPLC-MS (Method C): m/z = 378 (M+1); Rt = 3.90 min.

15

Example 269 (General procedure (C))**N-{4-[2-(2,4-Dioxothiazolidin-5-ylidenemethyl)-phenoxy]-phenyl}-acetamide**

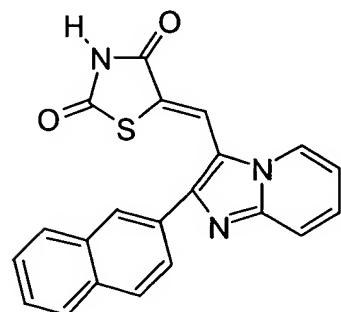
HPLC-MS (Method C): m/z = 355 (M+1); Rt. 3.33 min.

5

Example 270 (General procedure (C))**5-(2-Phenyl-imidazo[1,2-a]pyridin-3-ylmethylene)-thiazolidine-2,4-dione**

HPLC-MS (Method C): m/z = 322 (M+1); Rt. = 2.78 min.

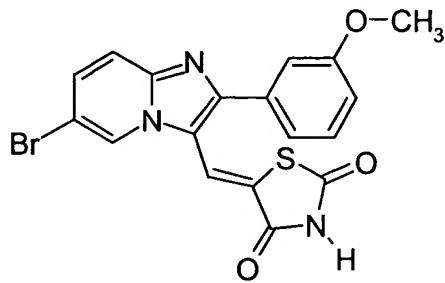
10

Example 271 (General procedure (C))**5-(2-Naphthalen-2-yl-imidazo[1,2-a]pyridin-3-ylmethylene)-thiazolidine-2,4-dione**

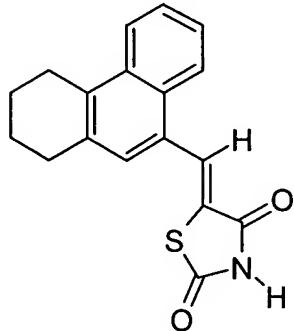
HPLC-MS (Method C): m/z = 372 (M+1); Rt. = 2.78 min.

15

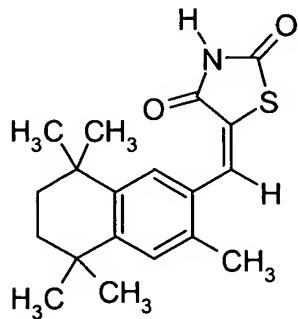
Example 272 (General procedure (C))

5-[6-Bromo-2-(3-methoxyphenyl)-imidazo[1,2-a]pyridin-3-ylmethylene]-thiazolidine-2,4-dione

HPLC-MS (Method C): m/z = 431 (M+1); Rt.= 3.30 min.

5 Example 273 (General procedure (C))**5-(1,2,3,4-Tetrahydrophenanthren-9-ylmethylene)thiazolidine-2,4-dione**

HPLC-MS (Method C): m/z = 310 (M+1); Rt.= 4.97 min.

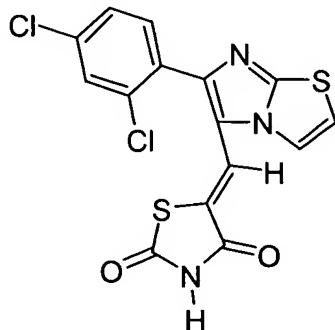
10 Example 274 (General procedure (C))**5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-ylmethylene)thiazolidine-2,4-dione**

HPLC-MS (Method C): m/z = 330 (M+1); Rt.= 5.33 min.

169

Example 275 (General procedure (C))

5-[6-(2,4-Dichloro-phenyl)-imidazo[2,1-b]thiazol-5-ylmethylene]-thiazolidine-2,4-dione

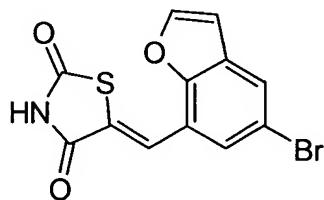


HPLC-MS (Method C): m/z = 396 (M+1); Rt. = 3.82 min.

5

Example 276 (General procedure (C))

5-(5-Bromobenzofuran-7-ylmethylene)-thiazolidine-2,4-dione

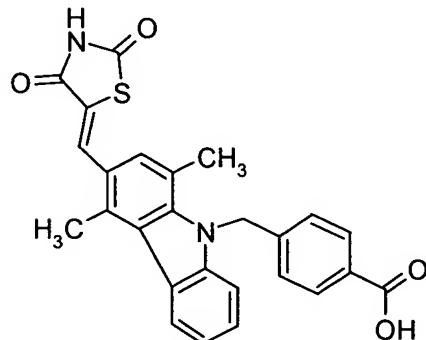


HPLC-MS (Method C): m/z = 324 (M+1); Rt. = 3.82 min.

10

Example 277 (General procedure (C))

4-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)-1,4-dimethylcarbazol-9-ylmethyl]-benzoic acid



HPLC-MS (Method C): m/z = 457 (M+1); Rt = 4.23 min.

15

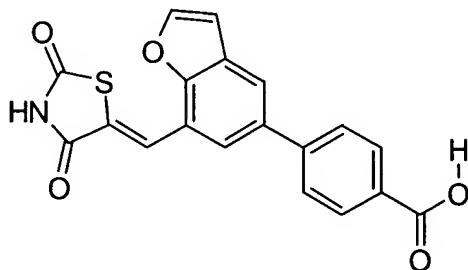
Preparation of intermediary aldehyde:

1,4 Dimethylcarbazol-3-carbaldehyde (0.68 g, 3.08 mmol) was dissolved in dry DMF (15 mL), NaH (diethyl ether washed) (0.162 g, 6.7 mol) was slowly added under nitrogen and the mixture was stirred for 1 hour at room temperature. 4-Bromomethylbenzoic acid (0.73 g, 3.4 mmol) was slowly added and the resulting slurry was heated to 40 °C for 16 hours. Water (5 mL) and hydrochloric acid (6N, 3 mL) were added. After stirring for 20 min at room temperature, the precipitate was filtered off and washed twice with acetone to afford after drying 0.38 g (34%) of 4-(3-formyl-1,4-dimethylcarbazol-9-ylmethyl)benzoic acid.

- 10 HPLC-MS (Method C) : m/z = 358 (M+1), RT. = 4.15 min.

Example 278 (General procedure (C))

4-[7-(2,4-Dioxothiazolidin-5-ylidenemethyl)-benzofuran-5-yl]-benzoic acid

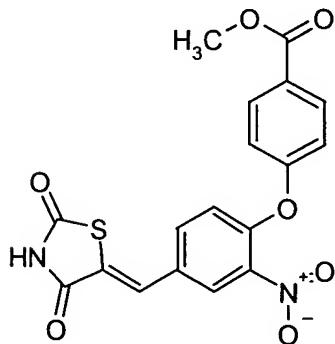


- 15 Starting aldehyde commercially available (Syncom BV, NL)

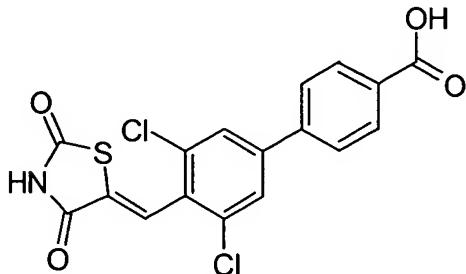
HPLC-MS (Method C): m/z = 366 (M+1); Rt. = 3.37 min.

Example 279 (General procedure (C))

4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-2-nitrophenoxy]-benzoic acid methyl ester

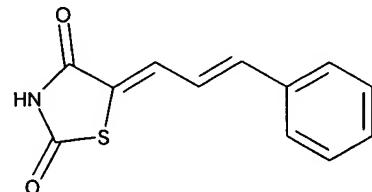


- 20 HPLC-MS (Method C): m/z = 401 (M+1); Rt. = 4.08 min.

Example 280 (General procedure (C))**3',5'-Dichloro-4'-(2,4-dioxothiazolidin-5-ylidenemethyl)-biphenyl-4-carboxylic acid**

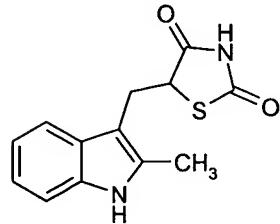
5 Starting aldehyde commercially available (Syncom BV, NL)

HPLC-MS (Method C): m/z = 394 (M+1); Rt. = 3.71 min.

Example 281 (General procedure (C))

10

HPLC-MS (Method C): m/z = 232 (M+1); Rt. = 3.6 min.

Example 282**5-(2-Methyl-1H-indol-3-ylmethyl)-thiazolidine-2,4-dione**

15

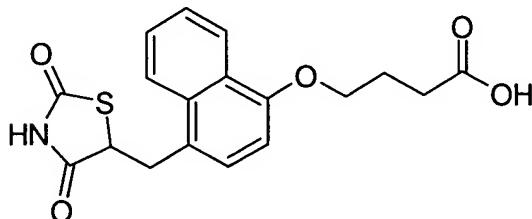
5-(2-Methyl-1H-indol-3-ylmethylene)thiazolidine-2,4-dione (prepared as described in example 187, 1.5 g, 5.8 mmol) was dissolved in pyridine (20 mL) and THF (50 mL), LiBH₄ (2 M in THF, 23.2 mmol) was slowly added with a syringe under cooling on ice. The mixture was heated to 85 °C for 2 days. After cooling, the mixture was acidified with concentrated

hydrochloric acid to pH 1. The aqueous layer was extracted 3 times with ethyl acetate, dried with MgSO₄ treated with activated carbon, filtered and the resulting filtrate was evaporated *in vacuo* to give 1.3 g (88%) of the title compound.

- 5 HPLC-MS (Method C): m/z = 261 (M+1); Rt. = 3.00 min.

Example 283

4-[4-(2,4-Dioxothiazolidin-5-ylmethyl)naphthalen-1-yloxy]butyric acid



- 10 4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyric acid (4.98 g, 13.9 mmol, prepared as described in example 469) was dissolved in dry THF (50 mL) and added dry pyridine (50 mL) and, in portions, lithium borohydride (2.0 M, in THF, 14 mL). The resulting slurry was refluxed under nitrogen for 16 hours, added (after cooling) more lithium borohydride (2.0 M, in THF, 7 mL). The resulting mixture was refluxed under nitrogen for 16 hours. The mixture was cooled and added more lithium borohydride (2.0 M, in THF, 5 mL). The resulting mixture was refluxed under nitrogen for 16 hours. After cooling to 5 °C, the mixture was added water (300 mL) and hydrochloric acid (150 mL). The solid was isolated by filtration, washed with water (3 x 500 mL) and dried. Recrystallization from acetonitrile (500 mL) afforded 2.5 g of the title compound.
- 15

20

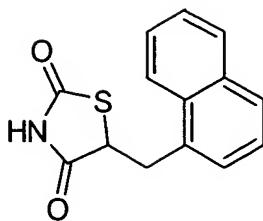
¹H-NMR (DMSO-*d*₆, selected peaks): δ = 3.42 (1H, dd), 3.90 (1H, dd), 4.16 (2H, "t"), 4.95 (1H, dd), 6.92 (1H, d), 7.31 (1H, d), 7.54 (1H, t), 7.62 (1H, t), 8.02 (1H, d), 8.23 (1H, d), 12.1 (1H, bs), 12.2 (1H, bs).

HPLC-MS (Method C): m/z = 382 (M+23); Rt = 3.23 min.

25

Example 284

5-Naphthalen-1-ylmethythiazolidine-2,4-dione



5-Naphthalen-1-ylmethylenethiazolidine-2,4-dione (1.08 g, 4.2 mmol, prepared as described in example 68) was dissolved in dry THF (15 mL) and added dry pyridine (15 mL) and, in portions, lithium borohydride (2.0 M, in THF, 4.6 mL). The resulting mixture was refluxed

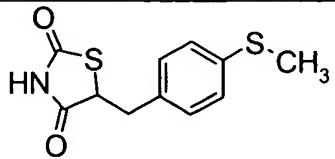
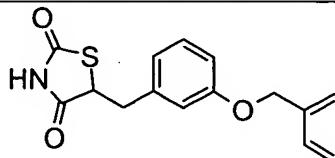
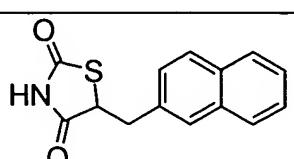
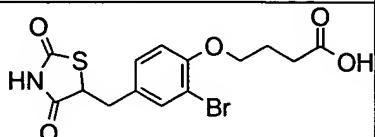
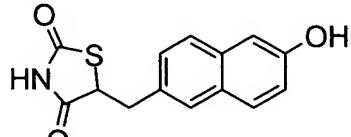
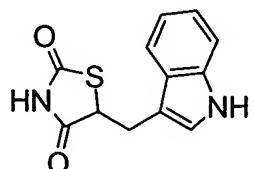
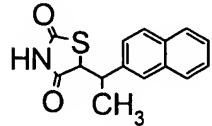
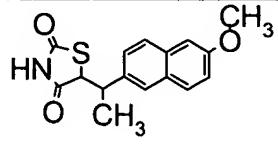
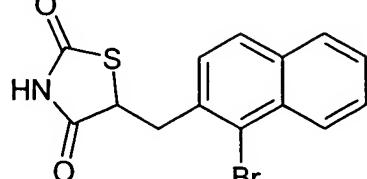
- 5 under nitrogen for 16 hours. After cooling to 5 °C, the mixture was added water (100 mL), and, in portions, concentrated hydrochloric acid (40 mL). More water (100 mL) was added, and the mixture was extracted with ethyl acetate (200 mL). The organic phase was washed with water (3 x 100 mL), dried and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (50 mL) added activated carbon, filtered and concentrated *in vacuo* and dried to afford 0.82 g (75%) of the title compound.

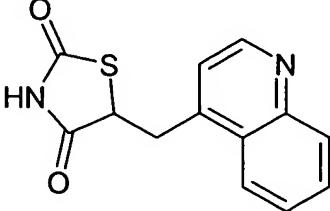
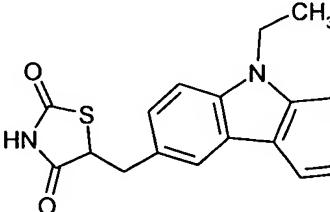
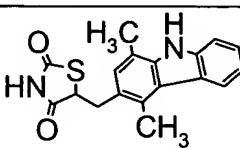
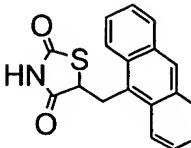
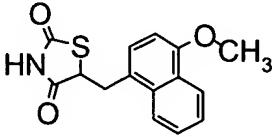
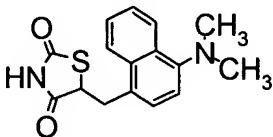
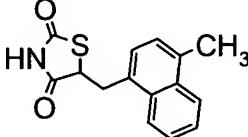
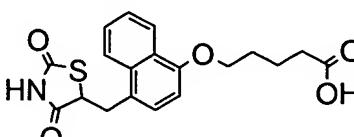
¹H-NMR (DMSO-*d*₆): δ = 3.54 (1H, dd), 3.98 (1H, dd), 5.00 (1H, dd), 7.4-7.6 (4H, m), 7.87 (1H, d), 7.96 (1H, d), 8.11 (1H, d), 12.2 (1H, bs).

HPLC-MS (Method C): m/z = 258 (M+1); Rt = 3,638 min.

- 15 The following preferred compounds of the invention may be prepared according to procedures similar to those described in the three examples above:

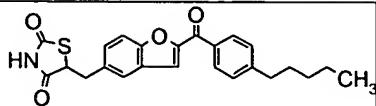
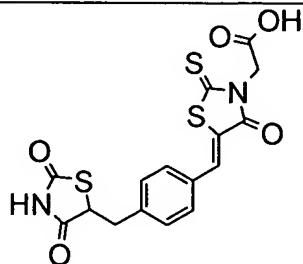
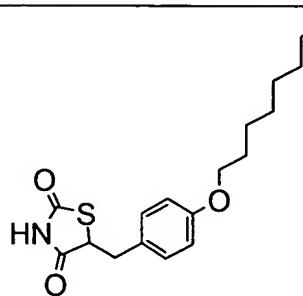
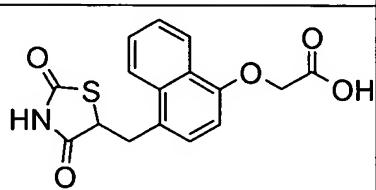
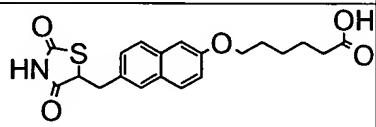
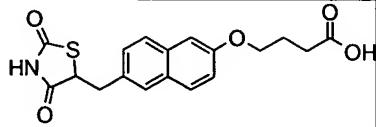
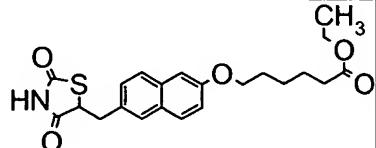
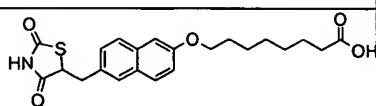
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Example 287		

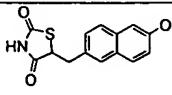
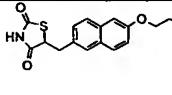
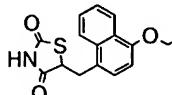
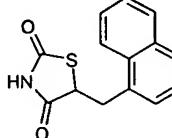
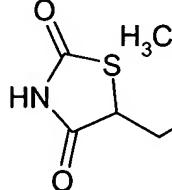
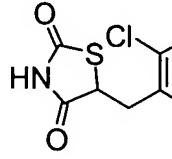
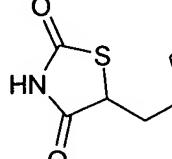
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Example 304		

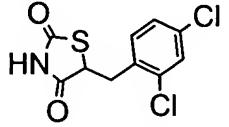
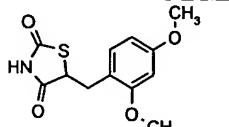
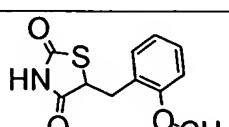
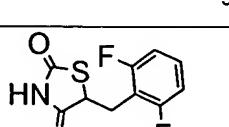
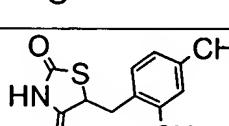
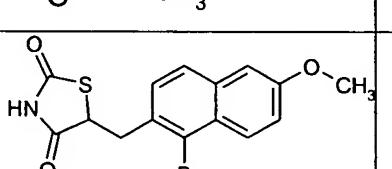
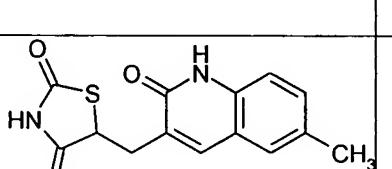
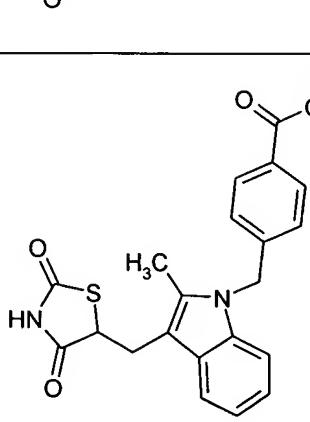
Example 305		
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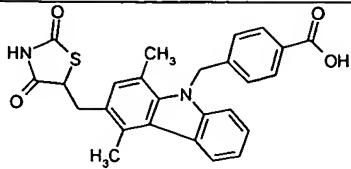
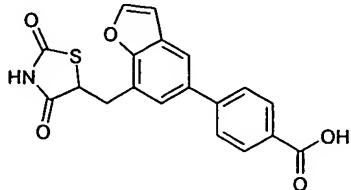
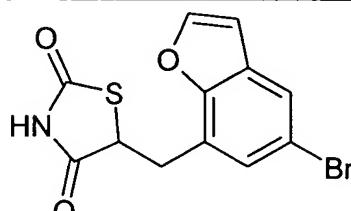
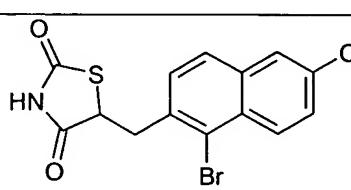
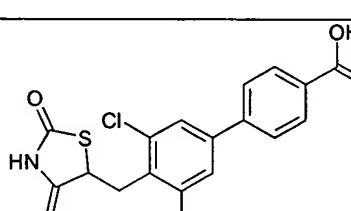
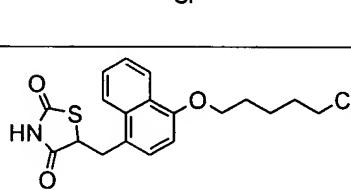
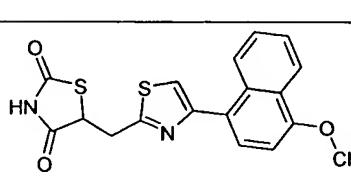
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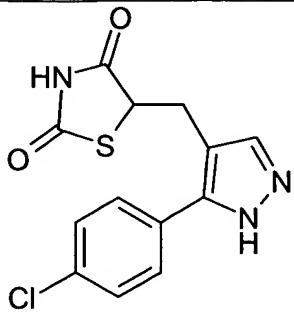
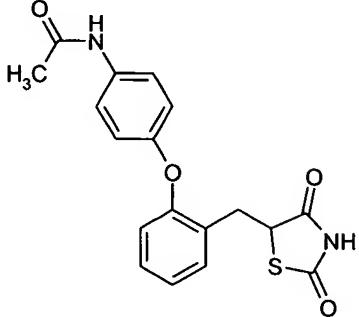
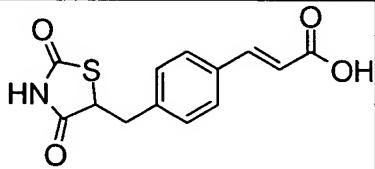
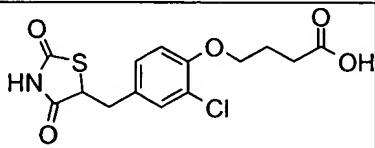
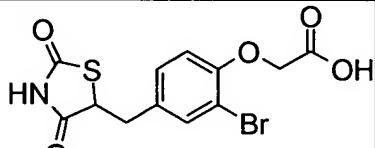
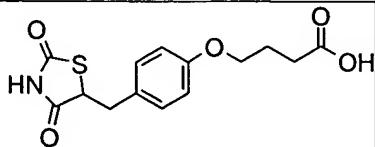
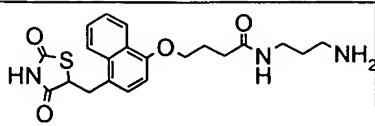
Example 329		
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Example 342		
Example 343		
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Example 345		
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Example 352		

Example 353	<p>Chemical structure of Example 353: A propanethioamide derivative where the propyl group is substituted at the 2-position with a 2,4-dichlorophenyl group and at the 3-position with a 5-bromo-2-chlorophenyl group.</p>
Example 354	<p>Chemical structure of Example 354: A propanethioamide derivative where the propyl group is substituted with a 2-phenylpropyl group.</p>
Example 355	<p>Chemical structure of Example 355: A propanethioamide derivative where the propyl group is substituted with a 2-methoxyphenyl group.</p>
Example 356	<p>Chemical structure of Example 356: A propanethioamide derivative where the propyl group is substituted with a 2-hydroxyphenyl group.</p>
Example 357	<p>Chemical structure of Example 357: A propanethioamide derivative where the propyl group is substituted with a 2-bromo-4-methylcyclopentyl group.</p>
Example 358	<p>Chemical structure of Example 358: A propanethioamide derivative where the propyl group is substituted with a 2-(2-oxoheptanoyloxy)-1,3-dihydrophthalimido group.</p>
Example 359	<p>Chemical structure of Example 359: A propanethioamide derivative where the propyl group is substituted with a 2-(2-hydroxybutyryloxy)-1,3-dihydrophthalimido group.</p>

Example 360		
Example 361		
Example 362		
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Example 365		
Example 366		

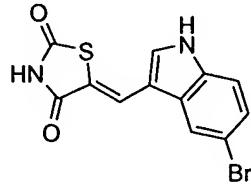
Example 367		
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Example 373		

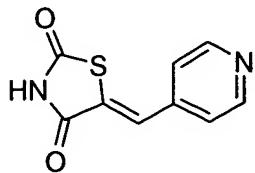
Example 374		
Example 375		
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Example 377		
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Example 379		

The following compounds are commercially available and may be prepared using general procedures (B) and / or (C).

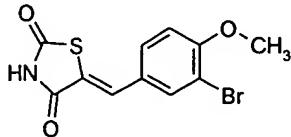
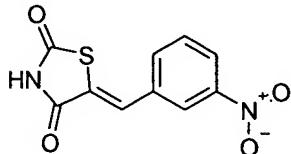
Example 380

- 5 5-(5-Bromo-1H-indol-3-ylmethylene)thiazolidine-2,4-dione

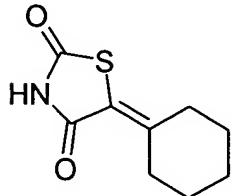


Example 381**5-Pyridin-4-ylmethylenethiazolidine-2,4-dione****Example 382**

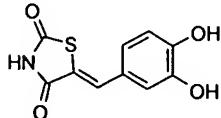
- 5 5-(3-Bromo-4-methoxybenzylidene)thiazolidine-2,4-dione

**Example 383****5-(3-Nitrobenzylidene)thiazolidine-2,4-dione**

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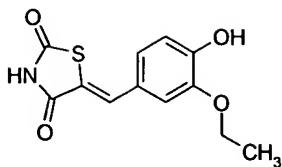
Example 384**5-Cyclohexylidene-1,3-thiazolidine-2,4-dione**

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Example 385**5-(3,4-Dihydroxybenzylidene)thiazolidine-2,4-dione**

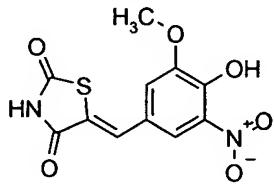
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Example 386**5-(3-Ethoxy-4-hydroxybenzylidene)thiazolidine-2,4-dione**



Example 387

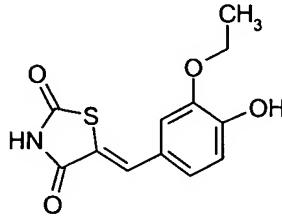
5-(4-Hydroxy-3-methoxy-5-nitrobenzylidene)thiazolidine-2,4-dione



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Example 388

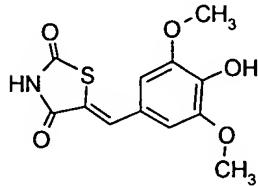
5-(3-Ethoxy-4-hydroxybenzylidene)thiazolidine-2,4-dione



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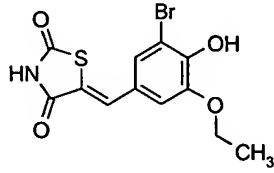
Example 389

5-(4-Hydroxy-3,5-dimethoxybenzylidene)thiazolidine-2,4-dione



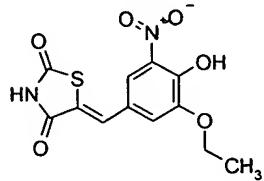
15 Example 390

5-(3-Bromo-5-ethoxy-4-hydroxybenzylidene)thiazolidine-2,4-dione

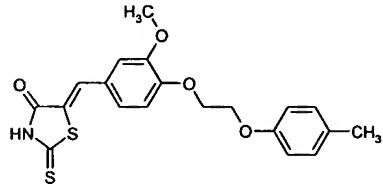


Example 391

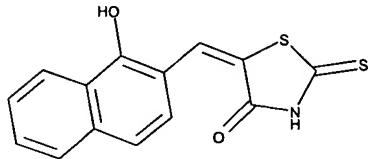
5-(3-Ethoxy-4-hydroxy-5-nitrobenzylidene)thiazolidine-2,4-dione



5 Example 392

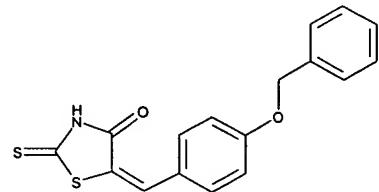


Example 393

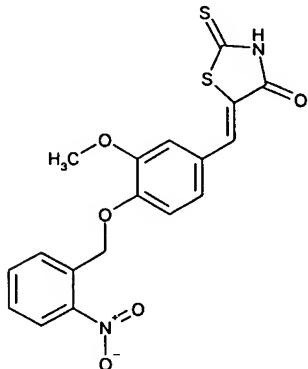


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Example 394

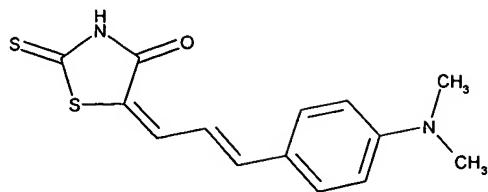


Example 395

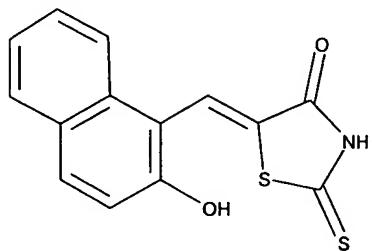


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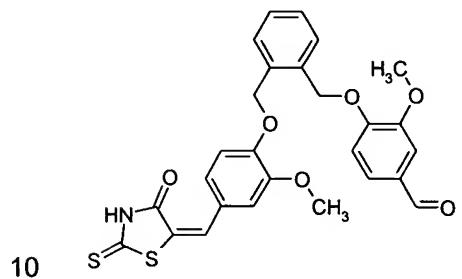
Example 396



5 Example 397

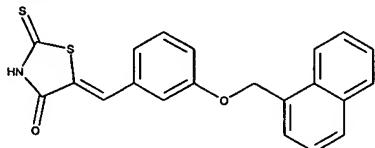


Example 398

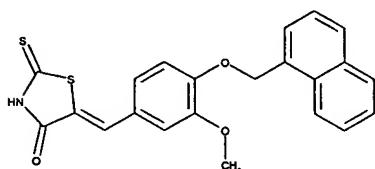


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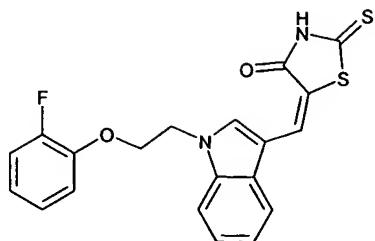
Example 399



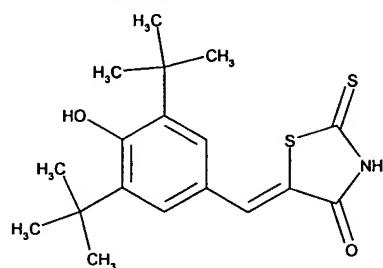
15 Example 400



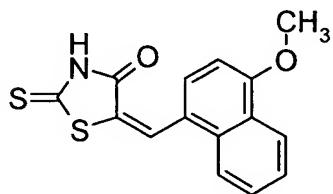
Example 401



5 Example 402

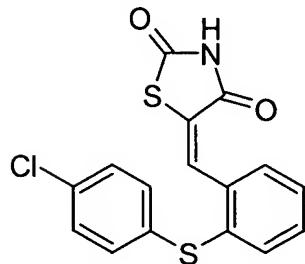


Example 403



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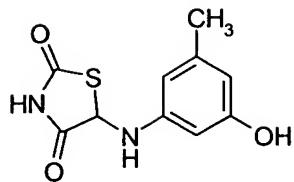
Example 404



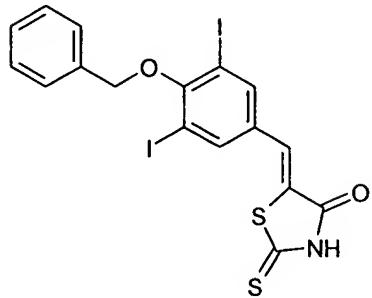
Example 405

15 5-(3-Hydroxy-5-methyl-phenylamino)-thiazolidine-2,4-dione

191

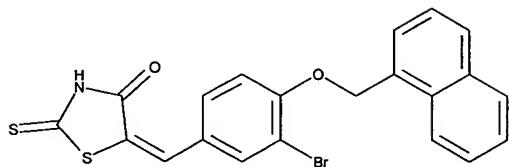


Example 406

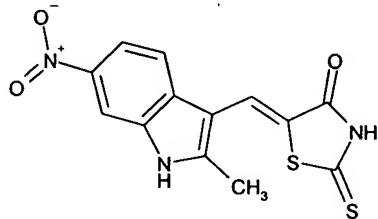


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Example 407



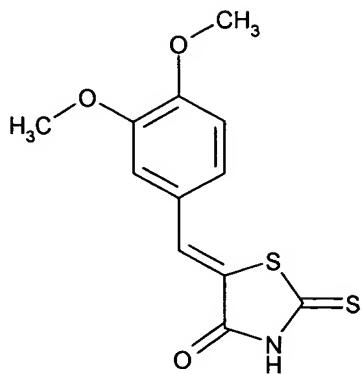
Example 408



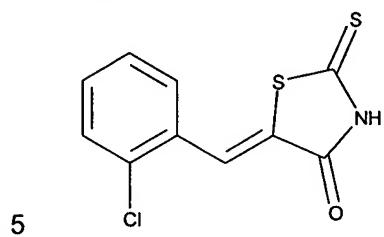
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192

Example 409

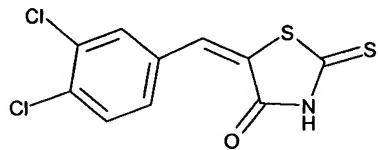


Example 410

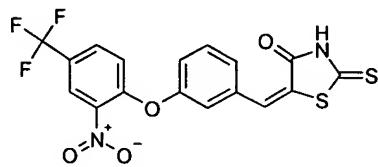


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Example 411

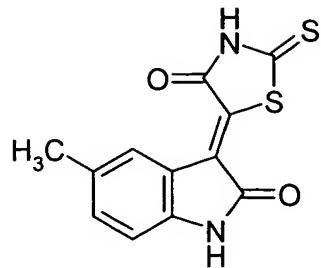


10 Example 412

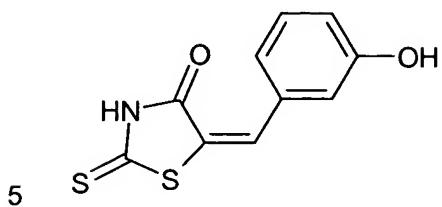


193

Example 413

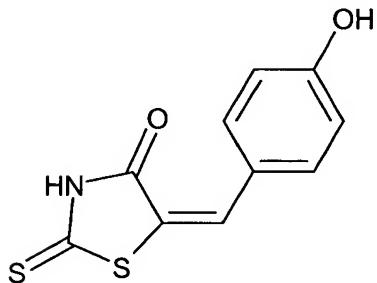


Example 414

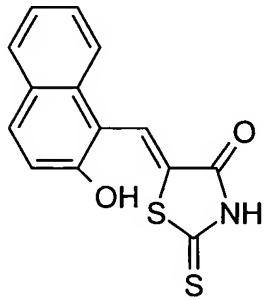


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Example 415

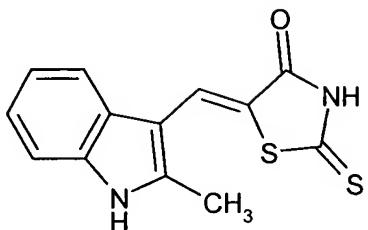


10 Example 416

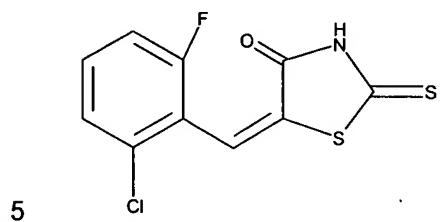


194

Example 417

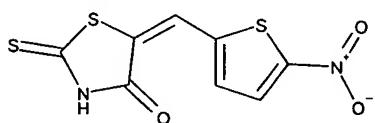


Example 418

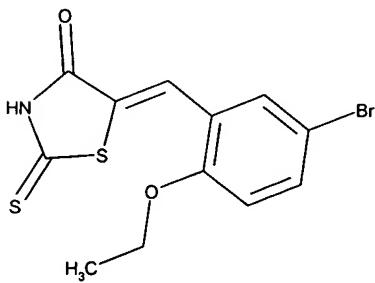


5

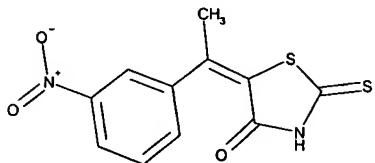
Example 419



10 Example 420

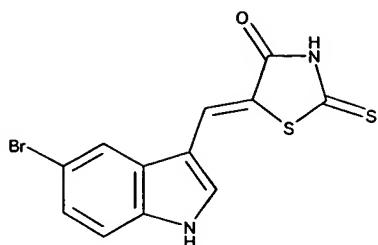


Example 421

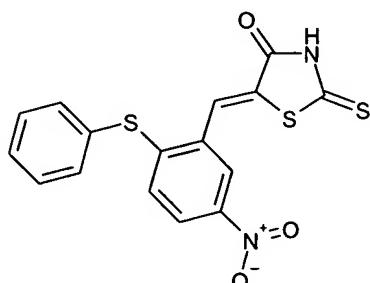


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Example 422

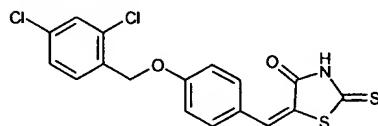


Example 423

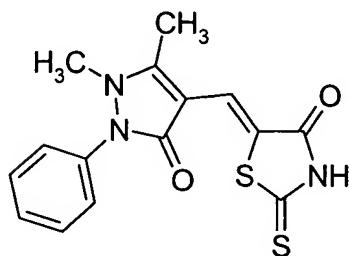


5

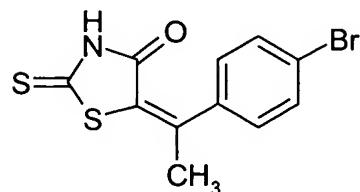
Example 424



10 Example 425

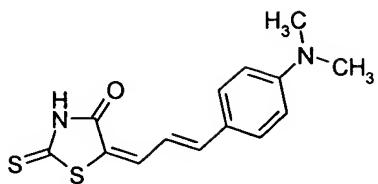


Example 426

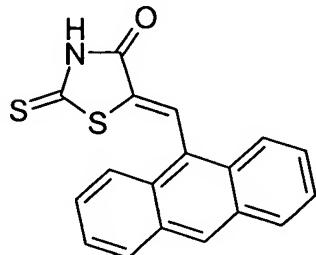


15

Example 427

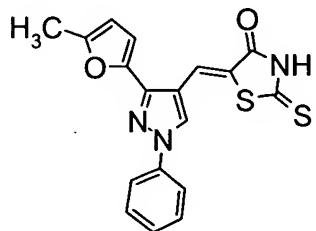


Example 428

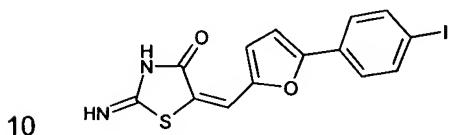


5

Example 429



Example 430

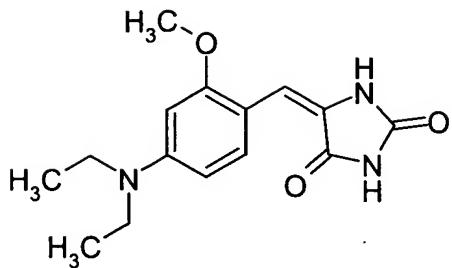


10

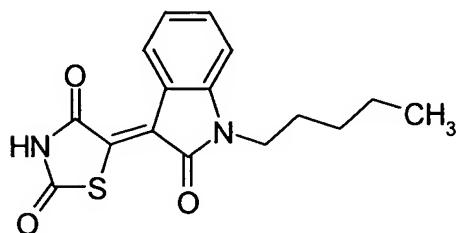
Example 431

5-(4-Diethylamino-2-methoxy-benzylidene)-imidazolidine-2,4-dione

197

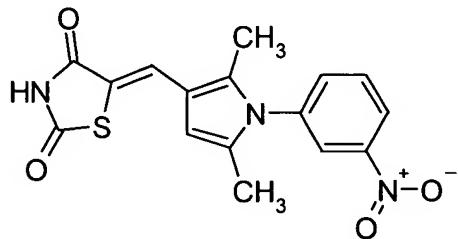


Example 432

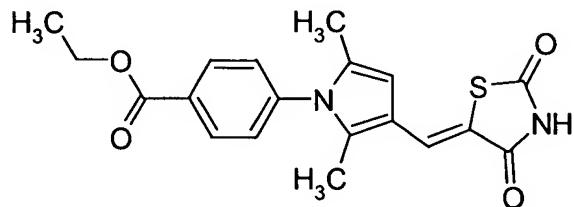


5

Example 433



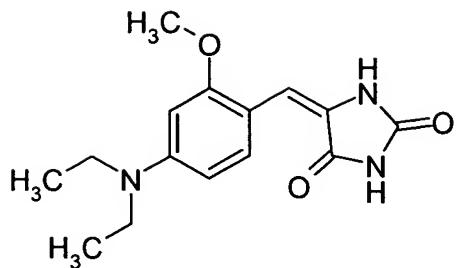
Example 434



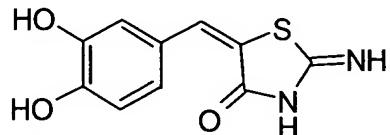
10

Example 435

198

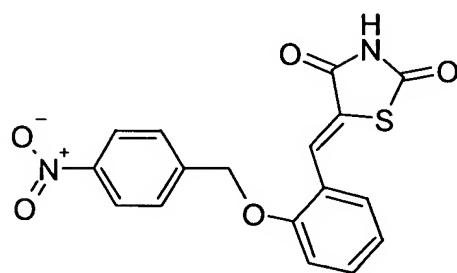


Example 436

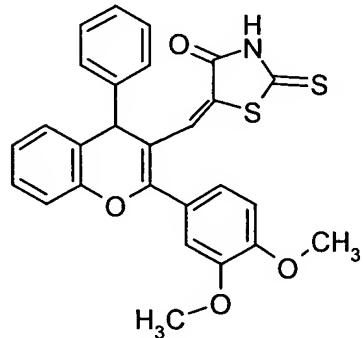


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Example 437



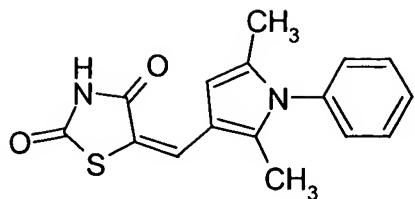
Example 438



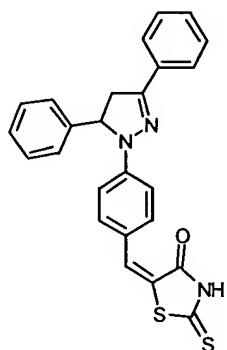
10

Example 439

199

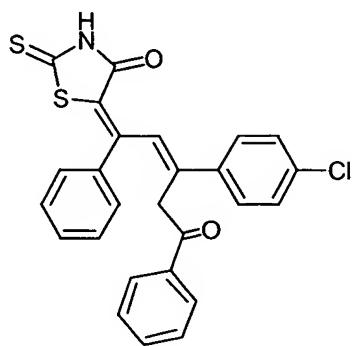


Example 440

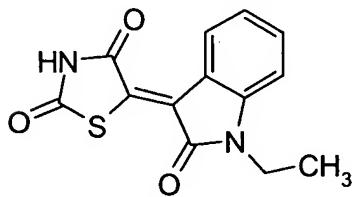


5

Example 441



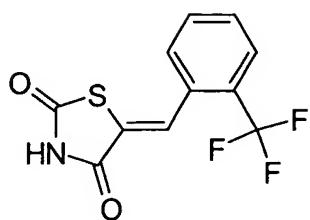
Example 442



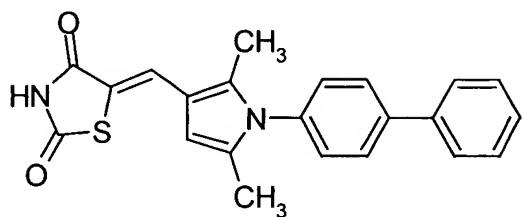
10

200

Example 443

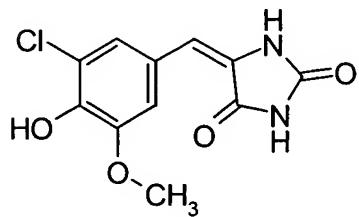


Example 444

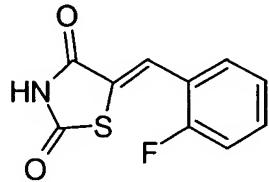


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Example 445

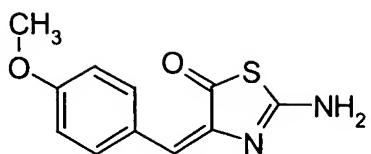


10 Example 446

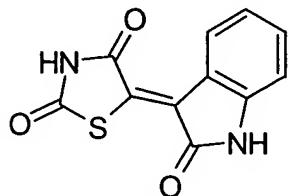


Example 447

201

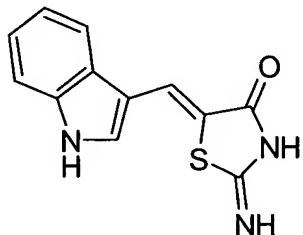


Example 448

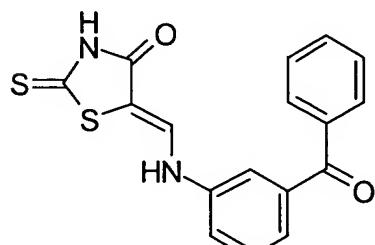


5

Example 449



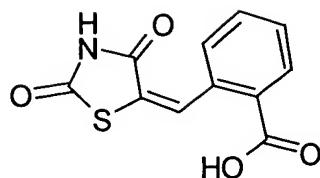
Example 450



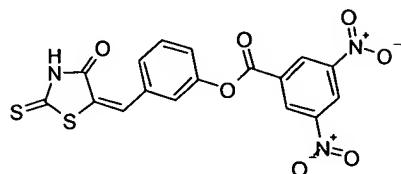
10

Example 451

202

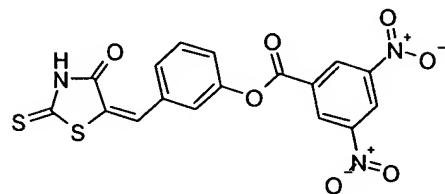


Example 452



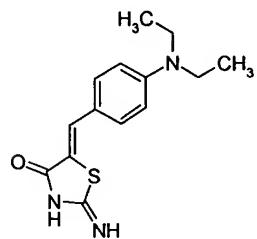
5

Example 453

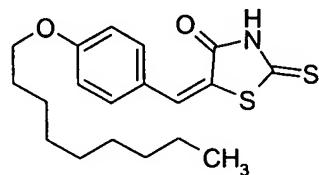


Example 454

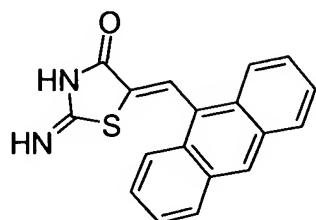
10 5-(4-Diethylamino-benzylidene)-2-imino-thiazolidin-4-one



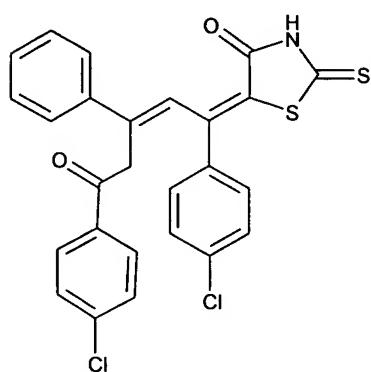
Example 455



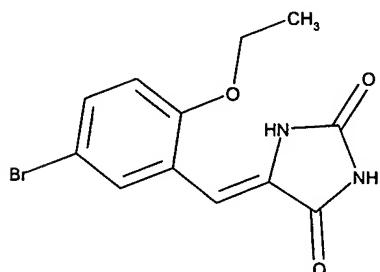
Example 456



5 Example 457

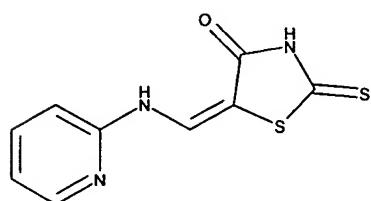


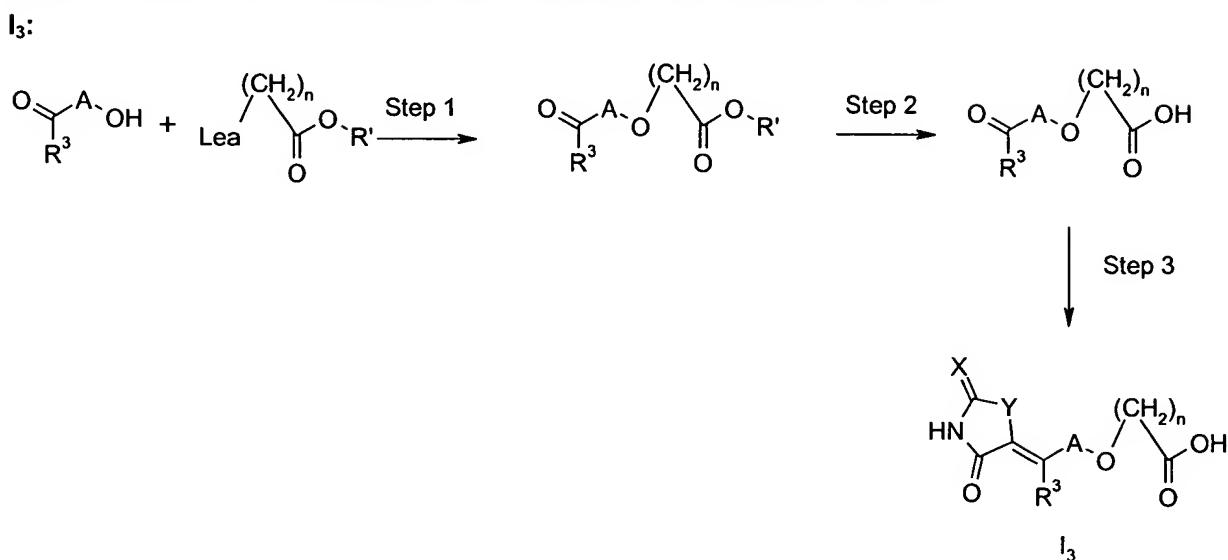
Example 458



10

Example 459



General procedure (D) for preparation of compounds of general formula I₃:

5

wherein X, Y, and R³ are as defined above,

n is 1 or 3-20,

E is arylene or heterarylene (including up to four optional substituents, R¹³, R¹⁴, R¹⁵, and R^{15A} as defined above),

- 10 R' is a standard carboxylic acid protecting group, such as C₁-C₆-alkyl or benzyl and Lea is a leaving group, such as chloro, bromo, iodo, methanesulfonyloxy, toluenesulfonyloxy or the like.

Step 1 is an alkylation of a phenol moiety. The reaction is performed by reacting R¹⁰-C(=O)-

- 15 E-OH with an ω -bromo-alkane-carboxylic acid ester (or a synthetic equivalent) in the presence of a base such as sodium or potassium carbonate, sodium or potassium hydroxide, sodium hydride, sodium or potassium alkoxide in a solvent, such as DMF, NMP, DMSO, acetone, acetonitrile, ethyl acetate or isopropyl acetate. The reaction is performed at 20 – 160 °C, usually at room temperature, but when the phenol moiety has one or more
20 substituents heating to 50 °C or more can be beneficial, especially when the substituents are in the ortho position relatively to the phenol. This will readily be recognised by those skilled in the art.

Step 2 is a hydrolysis of the product from step 1.

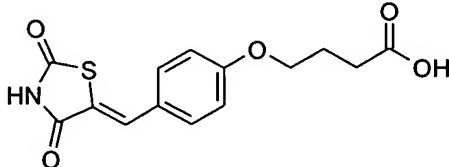
Step 3 is similar to general procedure (B) and (C).

This general procedure (D) is further illustrated in the following examples:

5

Example 460 (General procedure (D))

4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid



Step 1:

- 10 A mixture of 4-hydroxybenzaldehyde (9.21 g, 75 mmol), potassium carbonate (56 g, 410 mmol) and 4-bromobutyric acid ethyl ester (12.9 mL, 90 mmol) in *N,N*-dimethylformamide (250 mL) was stirred vigorously for 16 hours at room temperature. The mixture was filtered and concentrated *in vacuo* to afford 19.6 g (100%) of 4-(4-formylphenoxy)butyric acid ethyl ester as an oil. $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 1.21 (3H, t), 2.05 (2H, p), 2.49 (2H, t), 4.12 (4H, m), 7.13 (2H, d), 7.87 (2H, d), 9.90 (1H, s). HPLC-MS (Method A): m/z = 237 (M+1); R_t = 3.46 min.
- 15

Step 2:

- 20 4-(4-Formylphenoxy)butyric acid ethyl ester (19.6 g, 75 mmol) was dissolved in methanol (250 mL) and 1N sodium hydroxide (100 mL) was added and the resulting mixture was stirred at room temperature for 16 hours. The organic solvent was evaporated *in vacuo* (40 °C, 120 mBar) and the residue was acidified with 1N hydrochloric acid (110 mL). The mixture was filtered and washed with water and dried *in vacuo* to afford 14.3 g (91%) 4-(4-formylphenoxy)butyric acid as a solid. $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 1.99 (2H, p), 2.42 (2H, t), 4.13 (2H, t), 7.14 (2H, d), 7.88 (2H, d), 9.90 (1H, s), 12.2 (1H, bs). HPLC-MS (Method A): m/z = 209 (M+1); R_t = 2.19 min.
- 25

Step 3:

- 30 Thiazolidine-2,4-dione (3.55 g, 27.6 mmol), 4-(4-formylphenoxy)butyric acid (5.74 g, 27.6 mmol), anhydrous sodium acetate (11.3 g, 138 mmol) and acetic acid (100 mL) was refluxed for 16 h. After cooling, the mixture was filtered and washed with acetic acid and water. Drying

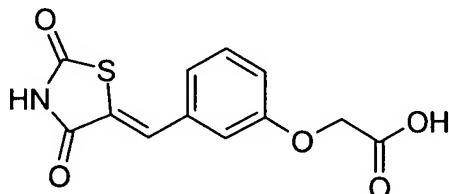
in vacuo afforded 2.74 g (32%) of 4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid as a solid.

¹H-NMR (DMSO-d₆): δ 1.97 (2H, p), 2.40 (2H, t), 4.07 (2H, t), 7.08 (2H, d), 7.56 (2H, d), 7.77 (1H, s), 12.2 (1H, bs), 12.5 (1H, bs); HPLC-MS (Method A): m/z: 308 (M+1); R_t = 2.89 min.

5

Example 461 (General procedure (D))

[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenoxy]acetic acid



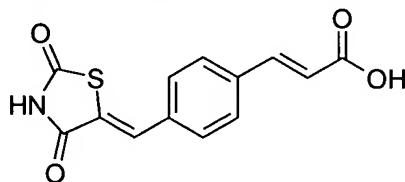
Step 3:

- 10 Thiazolidine-2,4-dione (3.9 g, 33 mmol), 3-formylphenoxyacetic acid (6.0 g, 33 mmol), anhydrous sodium acetate (13.6 g, 165 mmol) and acetic acid (100 mL) was refluxed for 16 h. After cooling, the mixture was filtered and washed with acetic acid and water. Drying in vacuo afforded 5.13 g (56%) of [3-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]acetic acid as a solid.
- 15 ¹H-NMR (DMSO-d₆): δ 4.69 (2H, s), 6.95 (1H, dd), 7.09 (1H, t), 7.15 (1H, d), 7.39 (1H, t), 7.53 (1H, s); HPLC-MS (Method A): m/z = 280 (M+1) (poor ionisation); R_t = 2.49 min.

The compounds in the following examples were similarly prepared.

- 20 Example 462 (General procedure (D))

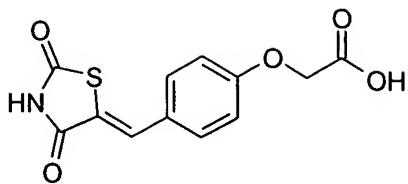
3-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenyl]acrylic acid



¹H-NMR (DMSO-d₆): δ 6.63 (1H, d), 7.59-7.64 (3H, m), 7.77 (1H, s), 7.83 (2H, m).

- 25 Example 463 (General procedure (D))

[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenoxy]acetic acid

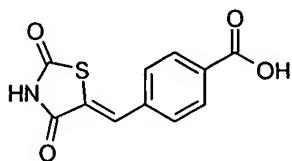


Triethylamine salt: $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 4.27 (2H, s), 6.90 (2H, d), 7.26 (1H, s), 7.40 (2H, d).

5

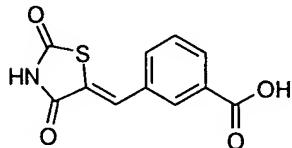
Example 464 (General procedure (D))

4-(2,4-Dioxothiazolidin-5-ylidenemethyl)benzoic acid



10 Example 465 (General procedure (D))

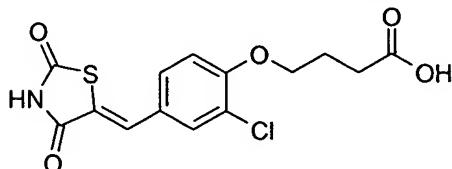
3-(2,4-Dioxothiazolidin-5-ylidenemethyl)benzoic acid



$^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 7.57 (1H, s), 7.60 (1H, t), 7.79 (1H, dt), 7.92 (1H, dt), 8.14 (1H, t).

15 Example 466 (General procedure (D))

4-[2-Chloro-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid



$^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 2.00 (2H, p), 2.45 (2H, t), 4.17 (2H, t), 7.31 (1H, d), 7.54 (1H, dd);

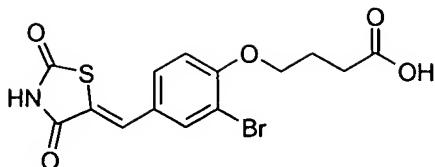
7.69 (1H, d), 7.74 (1H, s), 12.2 (1H, bs), 12.6 (1H, bs). HPLC-MS (Method A): m/z: 364

20 (M+23); Rt = 3.19 min.

Example 467 (General procedure (D))

4-[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid

208



¹H-NMR (DMSO-d₆): δ 1.99 (2H, p), 2.46 (2H, t), 4.17 (2H, t), 7.28 (1H, d), 7.57 (1H, dd), 7.25 (1H, s), 7.85 (1H, d), 12.2 (1H, bs), 12.6 (1H, bs). HPLC-MS (Method A): m/z: 410 (M+23); Rt = 3.35 min.

5

Example 468 (General procedure (D))

4-[2-Bromo-4-(4-oxo-2-thioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid

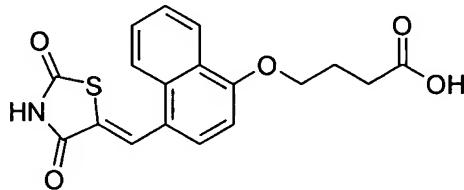


¹H-NMR (DMSO-d₆): δ 1.99 (2H, p), 2.45 (2H, t), 4.18 (2H, t), 7.28 (1H, d), 7.55 (1H, dd), 10 7.60 (1H, s), 7.86 (1H, d), 12.2 (1H, bs), 13.8 (1H, bs). HPLC-MS (Method A): m/z: 424 (M+23); Rt = 3.84 min.

HPLC-MS (Method A): m/z: 424 (M+23); Rt = 3.84 min

Example 469 (General procedure (D))

15 4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyric acid

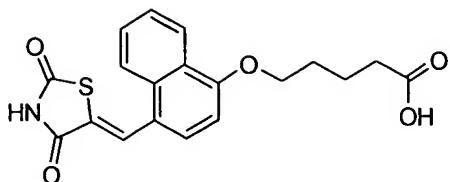


¹H-NMR (DMSO-d₆): δ 2.12 (2H, p), 2.5 (below DMSO), 4.28 (2H, t), 7.12 (1H, d), 7.6-7.7 (3H, m), 8.12 (1H, d), 8.31 (1H, d), 8.39 (1H, s), 12.2 (1H, bs), 12.6 (1H, bs). HPLC-MS (Method A): m/z: 380 (M+23); Rt = 3.76 min.

20

Example 470 (General procedure (D))

5-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]pentanoic acid



HPLC-MS (Method A): m/z: 394 (M+23); Rt = 3.62 min.

¹H-NMR (DMSO-d₆): δ 1.78 (2H, m), 1.90 (2H, m), 2.38 (2H, t), 4.27 (2H, t), 7.16 (1H, d), 7.6-7.75 (3H, m), 8.13 (1H, d), 8.28 (1H, d), 8.39 (1H, s), 12.1 (1H, bs), 12.6 (1H, bs).

5

Example 471

5-[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]pentanoic acid.



10 5-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]pentanoic acid (example 470, 185 mg, 0.5 mmol) was treated with an equimolar amount of bromine in acetic acid (10 mL). Stirring at RT for 14 days followed by evaporation to dryness afforded a mixture of the brominated compound and unchanged starting material. Purification by preparative HPLC on a C18 column using acetonitrile and water as eluent afforded 8 mg of the title compound.

15

HPLC-MS (Method C): m/z: 473 (M+23), Rt. = 3.77 min

Example 472

4-[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyric acid.



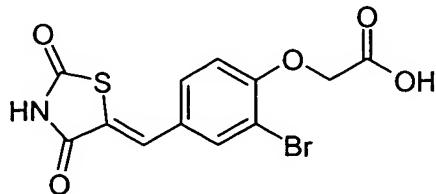
20

Starting with 4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]butyric acid (example 469, 0.5 mmol) using the same method as in example 471 afforded 66 mg of the title compound.

25 HPLC-MS (Method C): m/z: 459 (M+23) ; Rt. = 3.59 min.

Example 473 (General procedure (D))

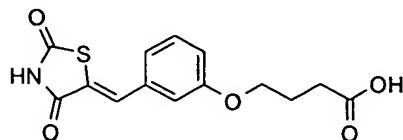
[2-Bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]acetic acid



- 5 $^1\text{H-NMR}$ (DMSO- d_6): δ 4.90 (2H, s), 7.12 (1H, d), 7.52 (1H, dd), 7.65 (1H, s) 7.84 (1H, d). HPLC-MS (Method A): m/z: not observed; Rt = 2.89 min.

Example 474 (General procedure (D))

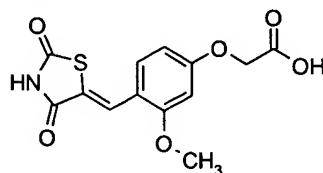
4-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenoxy]butyric acid



- 10 $^1\text{H-NMR}$ (DMSO- d_6): δ 1.98 (2H, p), 2.42 (2H, t), 4.04 (2H, t), 7.05 (1H, dd), 7.15 (2H, m), 7.45 (1H, t), 7.77 (1H, s), 12.1 (1H, bs), 12.6 (1H, bs). HPLC-MS (Method A): m/z: 330 (M+23); Rt = 3.05 min.

15 Example 475 (General procedure (D))

[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-3-methoxyphenoxy]acetic acid

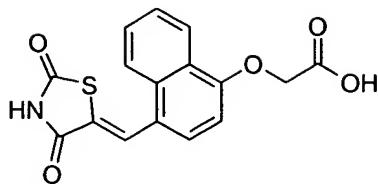


HPLC-MS (Method B): m/z: 310 (M+1); Rt = 3,43 min.

20

Example 476 (General procedure (D))

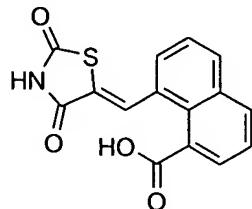
[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]acetic acid



HPLC-MS (Method A): m/z: 330 (M+1); Rt = 3.25 min.

Example 477 (General procedure (D))

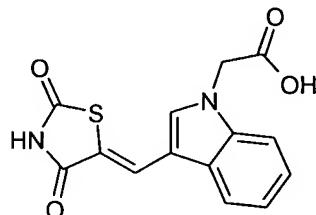
- 5 8-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalene-1-carboxylic acid



HPLC-MS (Method A): m/z: 299 (M+1); Rt = 2.49 min.

Example 478 (General procedure (D))

- 10 [3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indol-1-yl]acetic acid



HPLC-MS (Method A): m/z: 303 (M+1); Rt = 2.90 min.

Preparation of starting material:

- 15 3-Formylindol (10 g, 69 mmol) was dissolved in *N,N*-dimethylformamide (100 mL) and under an atmosphere of nitrogen and with external cooling, keeping the temperature below 15 °C, sodium hydride (60% in mineral oil, 3.0 g, 76 mmol) was added in portions. Then a solution of ethyl bromoacetate (8.4 mL, 76 mmol) in *N,N*-dimethylformamide (15 mL) was added dropwise over 30 minutes and the resulting mixture was stirred at room temperature for 16 hours. The mixture was concentrated *in vacuo* and the residue was partitioned between water (300 mL) and ethyl acetate (2 x 150 mL). The combined organic extracts were washed with a saturated aqueous solution of ammonium chloride (100 mL), dried ($MgSO_4$) and
- 20

concentrated in vacuo to afford 15.9 g (quant.) of (3-formylindol-1-yl)acetic acid ethyl ester as an oil.

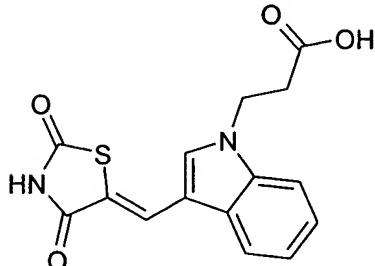
5 $^1\text{H-NMR}$ (CDCl_3): $\delta_{\text{H}} = 1.30$ (3H, t), 4.23 (2H, q), 4.90 (2H, s), 7.3 (3H, m), 7.77 (1H, s), 8.32 (1H, d), 10.0 (1H, s).

(3-Formylindol-1-yl)acetic acid ethyl ester (15.9 g 69 mmol) was dissolved in 1,4-dioxane (100 mL) and 1N sodium hydroxide (10 mL) was added and the resulting mixture was stirred at room temperature for 4 days. Water (500 mL) was added and the mixture was washed 10 with diethyl ether (150 mL). The aqueous phase was acidified with 5N hydrochloric acid and extracted with ethyl acetate (250 + 150 mL). The combined organic extracts were dried (MgSO_4) and concentrated in vacuo to afford 10.3 g (73%) of (3-formylindol-1-yl)acetic acid as a solid.

15 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): $\delta_{\text{H}} = 5.20$ (2H, s), 7.3 (2H, m), 7.55 (1H, d), 8.12 (1H, d), 8.30 (1H, s), 9.95 (1H, s), 13.3 (1H, bs).

Example 479 (General procedure (D))

3-[3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indol-1-yl]propionic acid



20 HPLC-MS (Method A): m/z: 317 (M+1); Rt = 3.08 min.

Preparation of starting material:

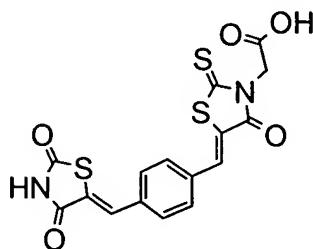
A mixture of 3-formylindol (10 g, 69 mmol), ethyl 3-bromopropionate (10.5 mL, 83 mmol) and 25 potassium carbonate (28.5 g, 207 mmol) and acetonitrile (100 mL) was stirred vigorously at reflux temperature for 2 days. After cooling, the mixture was filtered and the filtrate was concentrated *in vacuo* to afford 17.5 g (quant.) of 3-(3-formylindol-1-yl)propionic acid ethyl ester as a solid.

¹H-NMR (DMSO-d₆): δ_H = 1.10 (3H, t), 2.94 (2H, t), 4.02 (2H, q), 4.55 (2H, t), 7.3 (2H, m), 7.67 (1H, d), 8.12 (1H, d), 8.30 (1H, s), 9.90 (1H, s).

3-(3-Formylindol-1-yl)propionic acid ethyl ester (17.5 g 69 mmol) was hydrolysed as
5 described above to afford 12.5 g (83%) of 3-(3-formylindol-1-yl)propionic acid as a solid.

¹H-NMR (DMSO-d₆): δ_H = 2.87 (2H, t), 4.50 (2H, t), 7.3 (2H, m), 7.68 (1H, d), 8.12 (1H, d), 8.31 (1H, s), 9.95 (1H, s), 12.5 (1H, bs).

10 Example 480 (General procedure (D))
{5-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)benzylidene]-4-oxo-2-thioxothiazolidin-3-yl}acetic acid

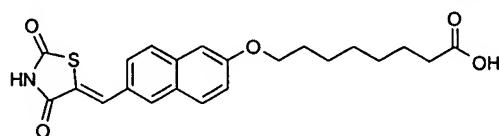


HPLC-MS (Method A): m/z: 429 (M+23); Rt = 3.89 min.

15 .

Example 481 (General procedure (D))

6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxyoctanoic acid



20 HPLC-MS (Method C): m/z: 436 (M+23); Rt.= 4.36 min

The intermediate aldehyde for this compound was prepared by a slightly modified procedure:
6-Hydroxynaphthalene-2-carbaldehyde (1.0 g, 5.8 mmol) was dissolved in DMF (10 mL) and sodium hydride 60% (278 mg) was added and the mixture stirred at RT for 15 min. 8-

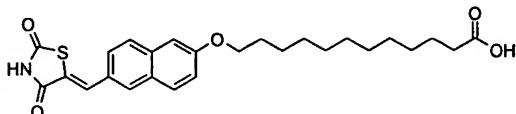
25 Bromooctanoic acid (0.37 g, 1.7 mmol) was converted to the sodium salt by addition of sodium hydride 60% and added to an aliquot (2.5 mL) of the above naphtholate solution and the resulting mixture was stirred at RT for 16 hours. Aqueous acetic acid (10 %) was added and the mixture was extracted 3 times with diethyl ether. The combined organic phases were

dried with MgSO₄ and evaporated to dryness affording 300 mg of 8-(6-formylnaphthalen-2-yloxy)octanoic acid.

HPLC-MS (Method C): m/z 315 (M+1); Rt. = 4.24 min.

5 Example 482 (General procedure (D))

12-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]dodecanoic acid.

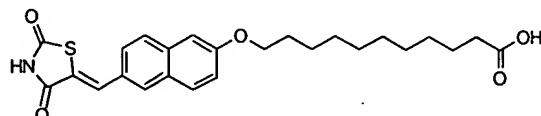


HPLC-MS (Method C): m/z: 492 (M+23); Rt.= 5.3 min.

- 10 The intermediate aldehyde was prepared similarly as described in example 481.

Example 483 (General procedure (D))

11-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]undecanoic acid.



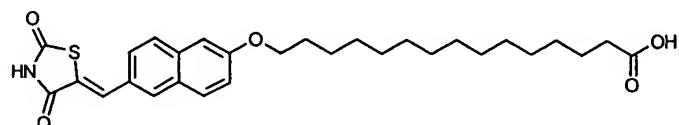
- 15

HPLC-MS (Method C): m/z:478 (M+23); Rt.= 5.17 min.

The intermediate aldehyde was prepared similarly as described in example 481.

- 20 Example 484 (General procedure (D))

15-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]pentadecanoic acid.

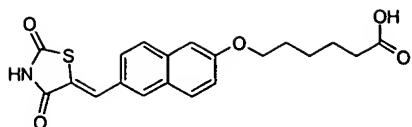


HPLC-MS (Method C): m/z: 534 (M+23); Rt.= 6.07 min.

- 25 The intermediate aldehyde was prepared similarly as described in example 481.

Example 485 (General procedure (D))

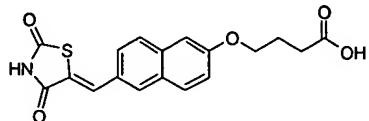
6-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]hexanoic acid.



HPLC-MS (Method C): m/z: 408 (M+23); Rt.= 3.71 min.

Example 486 (General procedure (D))

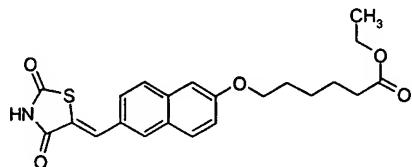
- 5 4-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]butyric acid.



HPLC-MS (Method C): m/z: 380 (M+23); Rt.= 3.23 min.

Example 487 (General procedure (D))

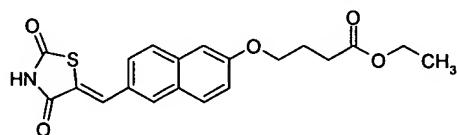
- 10 6-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]hexanoic acid ethyl ester.



HPLC-MS (Method C): m/z: 436 (M+23); Rt.= 4.64 min.

Example 488 (General procedure (D))

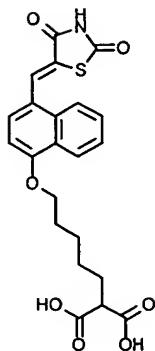
- 15 4-[6-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-2-yloxy]butyric acid ethyl ester.



HPLC-MS (Method C): m/z: 408 (M+23); Rt.= 4.28 min.

Example 489 (General procedure (D))

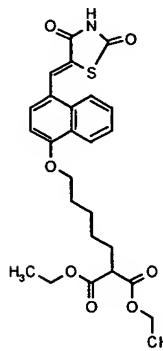
- 20 2-{5-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]pentyl}malonic acid



HPLC-MS (Method C): m/z = 444 (M+1); Rt = 3,84 min.

Example 490 (General procedure (D))

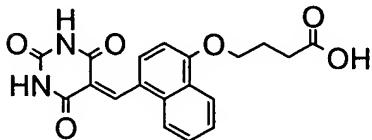
- 5 2-{5-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]pentyl}malonic acid diethyl ester



HPLC-MS (Method C): m/z = 500 (M+1); Rt = 5.18 min.

10 **Example 491 (General procedure (D))**

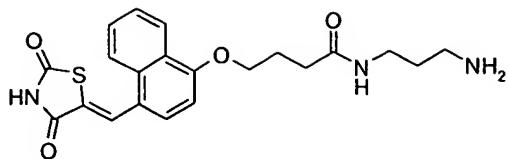
- 4-[4-(2,4,6-Trioxotetrahydropyrimidin-5-ylidenemethyl)naphthalen-1-yloxy]butyric acid



HPLC-MS (Method C): m/z = 369 (M+1); Rt = 2,68 min.

15 **Example 492**

- N-(3-Aminopropyl)-4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-butyramide



To a mixture of 4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyric acid (example 469, 5.9 g, 16.5 mmol) and 1-hydroxybenzotriazole (3.35 g, 24.8 mmol) in DMF (60 mL) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (4.75 g, 24.8 mmol) and the resulting mixture was stirred at room temperature for 2 hours. *N*-(3-amino-propyl)carbamic acid *tert*-butyl ester (3.45 g, 19.8 mmol) was added and the resulting mixture was stirred at room temperature for 16 hours. The mixture was concentrated *in vacuo* and ethyl acetate and dichloromethane were added to the residue. The mixture was filtered, washed with water and dried *in vacuo* to afford 4.98 g (59%) of (3-{4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyryl}amino)propyl carbamic acid *tert*-butyl ester.

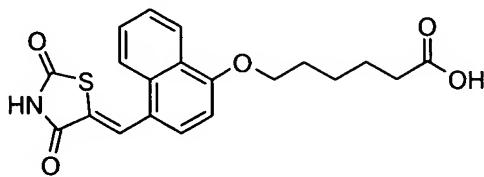
HPLC-MS (Method C): m/z: 515 (M+1); Rt = 3.79 min.

(3-{4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyryl}amino)-
propyl carbamic acid *tert*-butyl ester (4.9 g, 9.5 mmol) was added dichloromethane (50 mL)
and trifluoroacetic acid (50 mL) and the resulting mixture was stirred at room temperature for
45 minutes. The mixture was concentrated *in vacuo* and co-evaporated with toluene. To the
residue was added ethyl acetate (100 mL) and the mixture was filtered and dried *in vacuo* to
afford the title compound as the trifluoroacetic acid salt.

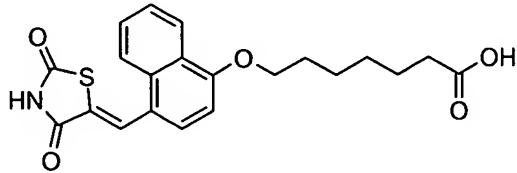
HPLC-MS (Method C): m/z: 414 (M+1); Rt = 2.27 min.

Compounds of the invention includes:

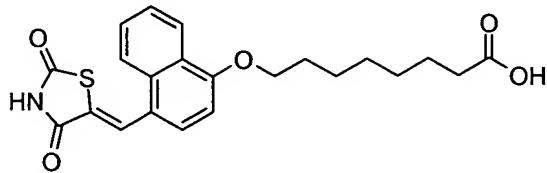
Example 493



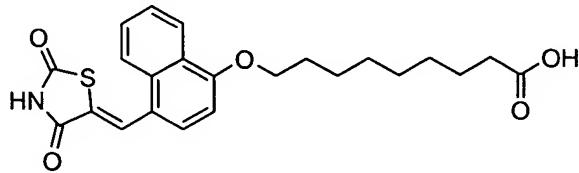
Example 494



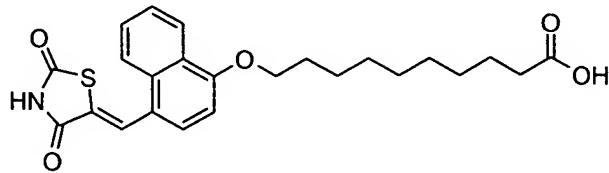
Example 495



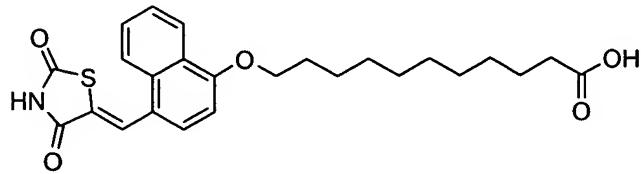
Example 496



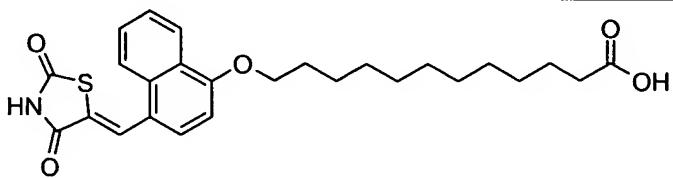
Example 497



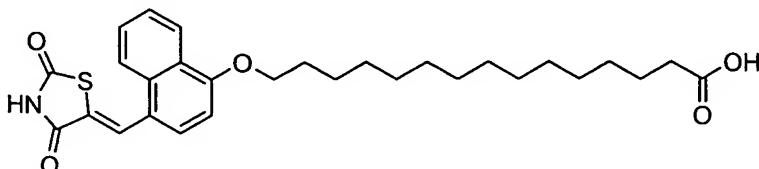
Example 498



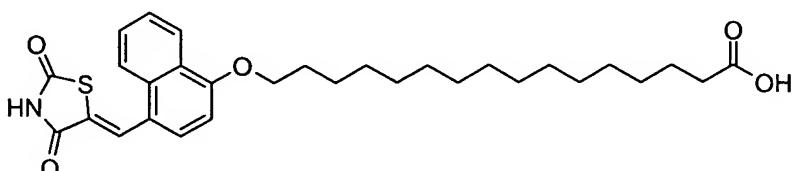
Example 499



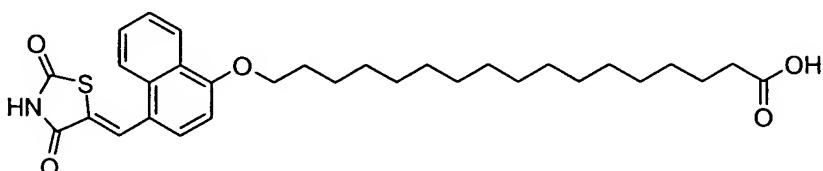
Example 500



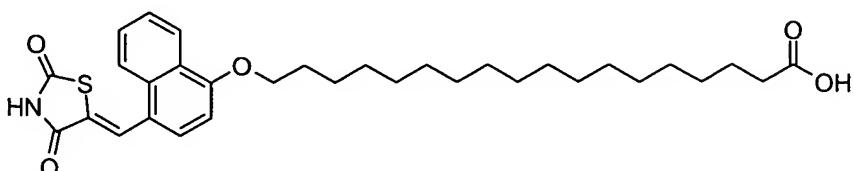
Example 501



Example 502

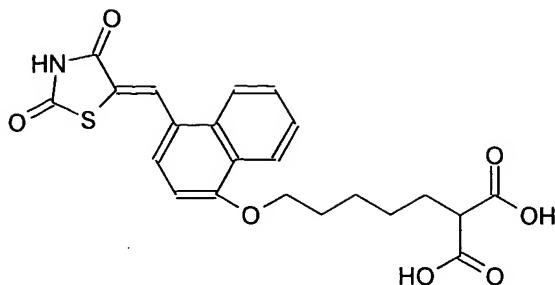


Example 503



Example 504 (Prepared analogously to General Procedure (D))

- 5 2-{5-[4-(2,4-Thiazolidindion-5-ylidenemethyl)naphthalen-1-yloxy]pentyl}malonic acid



A solution of 4-hydroxy-1-napthaldehyde (1.0 g, 5.81 mmol), 2-(5-bromopentyl)malonic acid diethyl ester (2.07 g, 6.68 mmol) and potassium carbonate (4.01 g, 29 mmol) in DMF (50 mL) was stirred at 100° C for 3 hours. The mixture was cooled and the salt was filtered off.

- 5 solvent was then removed under reduced pressure to afford 2.9 g of crude 2-[5-(4-formylnaphthalen-1-yloxy)pentyl]malonic acid diethyl ester which was used for the next reaction without further purification.

HPLC-MS (Method C): m/z: 401 (M+1); Rt = 5.16 min. ¹H-NMR (DMSO-d₆): δ = 1.18 (t, 6 H), 1.39 (m, 2 H), 1.55 (m, 2 H), 1.87 (m, 4 H), 3.48 (t, 1 H), 4.13 (m, 4 H), 4.27 (t, 2 H), 7.17 (d, 1 H), 7.64(t, 1 H), 7.75 (t, 1 H), 8.13 (d, 1 H), 8.29 (d, 1 H), 9.24 (d, 1 H), 10.19 (s, 1 H).

1.4 g (3.5 mmol) of crude 2-[5-(4-formylnaphthalen-1-yloxy)pentyl]malonic acid diethyl ester was treated with aqueous sodium hydroxide (1N, 8.75 mL, 8.75 mmol) and methanol (50 mL). The solution was stirred at 70° C for 5 hours and the mixture was concentrated under reduced pressure. Hydrochloric acid (6 N) was added until pH <2. The resulting slurry was stirred until it solidified. The crystals were filtered off, washed with water and then dried *in vacuo* to afford 1.1 g (92%) of 2-[5-(4-formylnaphthalen-1-yloxy)pentyl]malonic acid. The product was used in the next step without further purification.

20 HPLC-MS (Method C): m/z: 345 (M+1); Rt = 3.52 min. ¹H-NMR(DMSO-d₆): δ = 1.40 (m, 2 H), 1.55 (m, 2 H), 1.80 (m, 2 H), 1.90 (m, 2 H), 3.24 (t, 1 H), 4.29 (t, 2 H), 7.19 (d, 1 H), 7.64(t, 1 H), 7.75 (t, 1 H), 8.14 (d, 1 H), 8.30 (d, 1 H), 9.23 (d, 1 H), 10.18 (s, 1 H), 12.69 (s, 2 H).

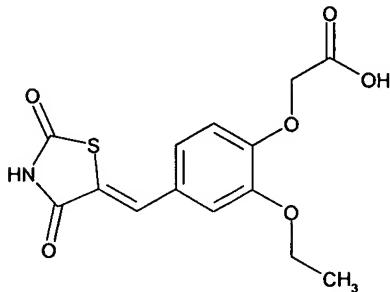
25 To a solution of 2-[5-(4-formylnaphthalen-1-yloxy) pentyl]malonic acid (0.36 g, 1.05 mmol) in acetic acid (10 mL) was added 2,4-thiazolidindione (0.16 g, 1.36 mmol) and piperidine (0.52 mL, 5.25 mmol). The solution was heated to 105 °C for 24 hours. After cooling to room temperature, the solvents were removed *in vacuo*. Water was added to the residue. The

precipitate was filtered off and washed with water. Recrystallisation from acetonitrile afforded 200 mg (43%) of the title compound as a solid.

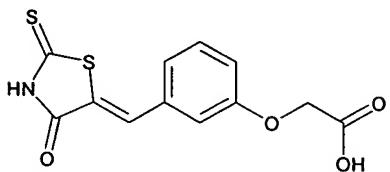
HPLC-MS (Method C): m/z: 422 (M-CO₂+Na); Rt = 4.08 min. ¹H-NMR(DMSO-d₆): δ = 1.41
5 (m, 2 H), 1.55 (m, 4 H), 1.88 (m, 2 H), 2.23 (t, 1 H), 4.24 (t, 2 H), 7.61-7.74 (m, 3 H), 8.12 (d, 1 H), 8.28 (d, 1 H), 8.38 (s, 1 H), 12.00 (s, 1 H), 12.59 (s, 2 H).

- 10 The following compounds are commercially available and may be prepared according to general procedure (D):

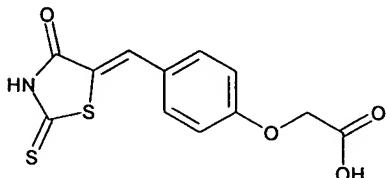
Example 505



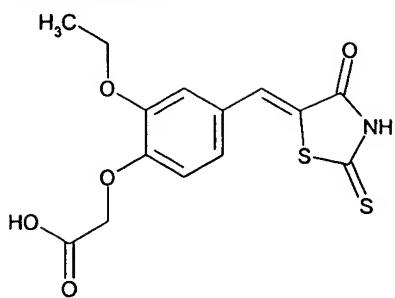
15 Example 506



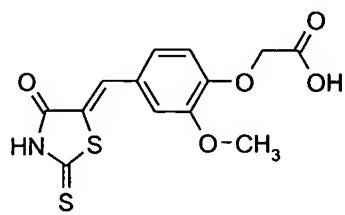
Example 507



Example 508

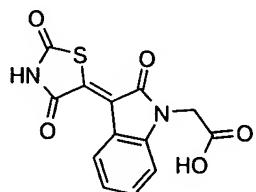


Example 509

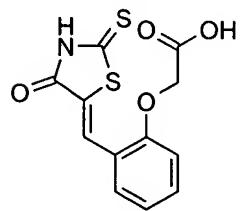


5

Example 510

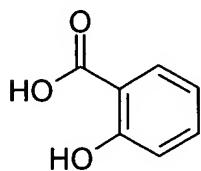
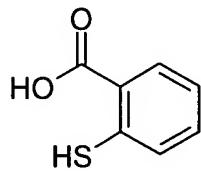
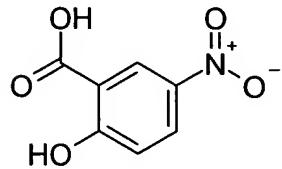
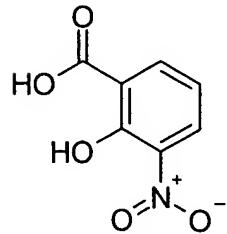


10 Example 511

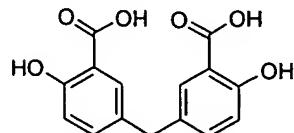


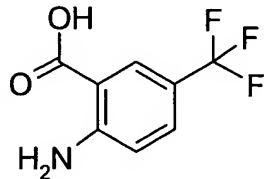
15

The following salicylic acid derivatives do all bind to the His B10 Zn²⁺ site of the insulin hexamer:

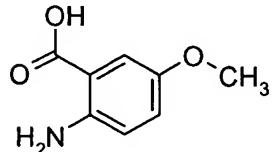
Example 512**Salicylic acid****5 Example 513****Thiosalicylic acid (or: 2-Mercaptobenzoic acid)****Example 514****10 2-Hydroxy-5-nitrobenzoic acid****Example 515****3-Nitrosalicylic acid**

15

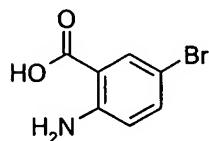
Example 516**5,5'-Methylenedisalicylic acid**

Example 517**2-Amino-5-trifluoromethylbenzoesyre**

5

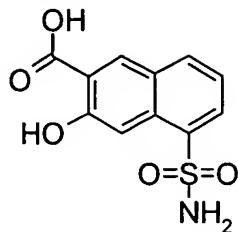
Example 518**2-Amino-4-chlorobenzoic acid**10 **Example 519****2-Amino-5-methoxybenzoesyre****Example 520**

15

**Example 521**

20

Example 522

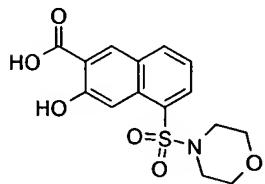


Example 523

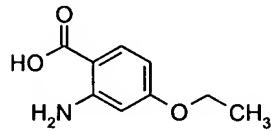


5

Example 524

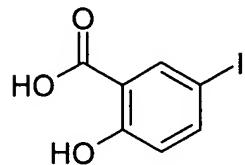


10 Example 525



Example 526

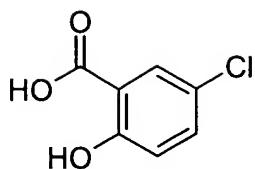
5-iodosalicylic acid



15

Example 527

5-Chlorosalicylic acid



Example 528

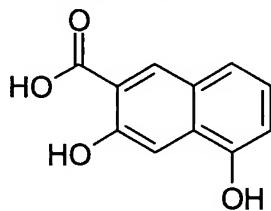
1-Hydroxy-2-naphthoic acid



5

Example 529

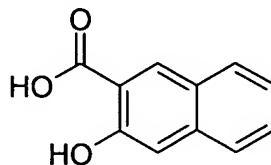
3,5-Dihydroxy-2-naphthoic acid



10

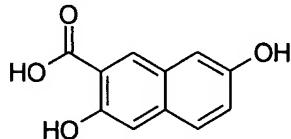
Example 530

3-Hydroxy-2-naphthoic acid



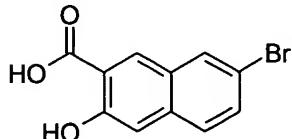
15 Example 531

3,7-Dihydroxy-2-naphthoic acid



Example 532

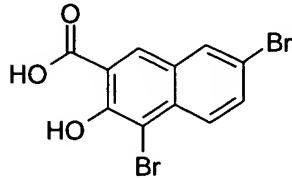
20 2-Hydroxybenzo[a]carbazole-3-carboxylic acid

**Example 533****7-Bromo-3-hydroxy-2-naphthoic acid**

5

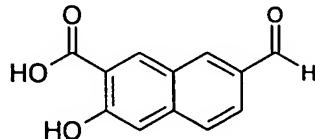
This compound was prepared according to Murphy *et al.*, *J. Med. Chem.* **1990**, *33*, 171-8.

HPLC-MS (Method A): m/z: 267 (M+1); Rt: = 3.78 min.

Example 534**10 1,6-Dibromo-2-hydroxynaphthalene-3-carboxylic acid**

This compound was prepared according to Murphy *et al.*, *J. Med. Chem.* **1990**, *33*, 171-8.

HPLC-MS (Method A): m/z: 346 (M+1); Rt: = 4.19 min.

15 Example 535**7-Formyl-3-hydroxynaphthalene-2-carboxylic Acid**

A solution of 7-bromo-3-hydroxynaphthalene-2-carboxylic acid (15.0 g, 56.2 mmol) (example 533) in tetrahydrofuran (100 mL) was added to a solution of lithium hydride (893 mg, 112 mmol) in tetrahydrofuran (350 mL). After 30 minutes stirring at room temperature, the resulting solution was heated to 50 °C for 2 minutes and then allowed to cool to ambient temperature over a period of 30 minutes. The mixture was cooled to -78 °C, and butyllithium (1.6 M in hexanes, 53 mL, 85 mmol) was added over a period of 15 minutes. *N,N*-

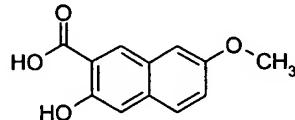
Dimethylformamide (8.7 mL, 8.2 g, 112 mmol) was added after 90 minutes additional stirring. The cooling was discontinued, and the reaction mixture was stirred at room temperature for 17 hours before it was poured into 1 N hydrochloric acid (aq.) (750 mL). The organic solvents were evaporated in vacuo, and the resulting precipitate was filtered off and rinsed with water (3 x 100 mL) to yield the crude product (16.2 g). Purification on silica gel (dichloromethane / methanol / acetic acid = 90:9:1) furnished the title compound as a solid.

¹H-NMR (DMSO-d₆): δ 11.95 (1H, bs), 10.02 (1H, s), 8.61 (1H, s), 8.54 (1H, s), 7.80 (2H, bs), 7.24 (1H, s); HPLC-MS (Method (A)): m/z: 217 (M+1); Rt = 2.49 min.

10

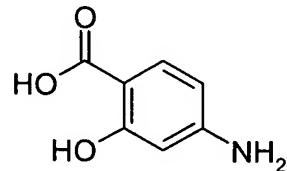
Example 536

3-Hydroxy-7-methoxy-2-naphthoic acid



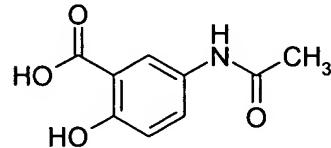
15 Example 537

4-Amino-2-hydroxybenzoic acid



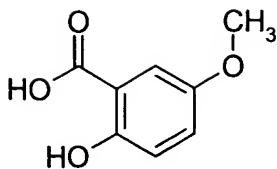
Example 538

20 5-Acetylamino-2-hydroxybenzoic acid



Example 539

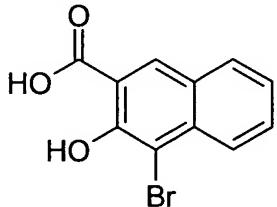
2-Hydroxy-5-methoxybenzoic acid



The following compounds were prepared as described below:

Example 540

- 5 4-Bromo-3-hydroxynaphthalene-2-carboxylic acid



3-Hydroxynaphthalene-2-carboxylic acid (3.0 g, 15.9 mmol) was suspended in acetic acid (40 mL) and with vigorous stirring a solution of bromine (817 μ L, 15.9 mmol) in acetic acid (10 mL) was added drop wise during 30 minutes. The suspension was stirred at room

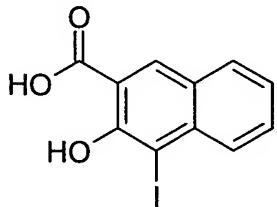
10 temperature for 1 hour, filtered and washed with water. Drying in vacuo afforded 3.74 g (88%) of 4-bromo-3-hydroxynaphthalene-2-carboxylic acid as a solid.

$^1\text{H-NMR}$ (DMSO- d_6): δ 7.49 (1H, t), 7.75 (1H, t), 8.07 (2H, "t"), 8.64 (1H, s). The substitution pattern was confirmed by a COSY experiment, showing connectivities between the 3 (4 hydrogen) "triplets". HPLC-MS (Method A): m/z: 267 (M+1); Rt = 3.73 min.

15

Example 541

- 3-Hydroxy-4-iodonaphthalene-2-carboxylic acid



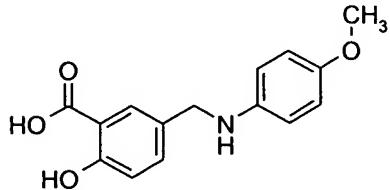
3-Hydroxynaphthalene-2-carboxylic acid (0.5 g, 2.7 mmol) was suspended in acetic acid (5 mL) and with stirring iodine monochloride (135 μ L, 2.7 mmol) was added. The suspension was stirred at room temperature for 1 hour, filtered and washed with water. Drying afforded 0.72 g (85%) of 4-iodo-3-hydroxynaphthalene-2-carboxylic acid as a solid.

$^1\text{H-NMR}$ (DMSO- d_6): δ 7.47 (1H, t), 7.73 (1H, t), 7.98 (1H, d), 8.05 (1H, d), 8.66 (1H, s).

HPLC-MS (Method A): m/z: 315 (M+1); Rt = 3.94 min.

Example 542

2-Hydroxy-5-[(4-methoxyphenylamino)methyl]benzoic acid



5

p-Anisidine (1.3 g, 10.6 mmol) was dissolved in methanol (20 mL) and 5-formylsalicylic acid (1.75 g, 10.6 mmol) was added and the resulting mixture was stirred at room temperature for 16 hours. The solid formed was isolated by filtration, re-dissolved in N-methyl pyrrolidone (20 mL) and methanol (2 mL). To the mixture was added sodium cyanoborohydride (1.2 g) and 10 the mixture was heated to 70 °C for 3 hours. To the cooled mixture was added ethyl acetate (100 mL) and the mixture was extracted with water (100 mL) and saturated aqueous ammonium chloride (100 mL). The combined aqueous phases were concentrated *in vacuo* and a 2 g aliquot was purified by SepPac chromatography eluting with mixtures of aetonitrile and water containing 0.1% trifluoroacetic acid to afford the title compound.

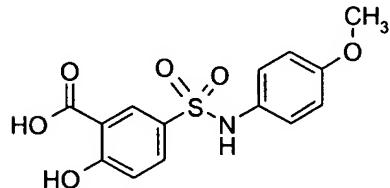
15

HPLC-MS (Method A): m/z: 274 (M+1); Rt = 1.77 min.

¹H-NMR (methanol-*d*₄): δ 3.82 (3H, s), 4.45 (2H, s), 6.96 (1H, d), 7.03 (2H, d), 7.23 (2H, d), 7.45 (1H, dd), 7.92 (1H, d).

20 Example 543

2-Hydroxy-5-(4-methoxyphenylsulfamoyl)benzoic acid



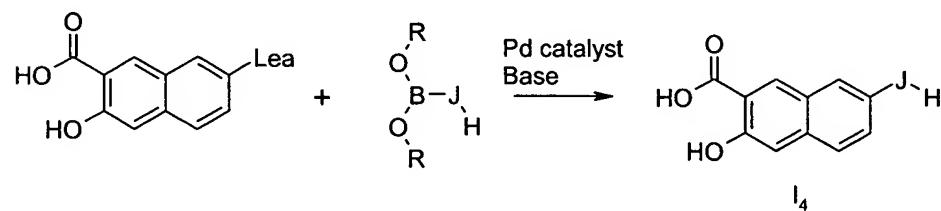
A solution of 5-chlorsulfonylsalicylic acid (0.96 g, 4.1 mmol) in dichloromethane (20 mL) and 25 triethylamine (1.69 mL, 12.2 mmol) was added p-anisidine (0.49 g, 4.1 mmol) and the resulting mixture was stirred at room temperature for 16 hours. The mixture was added dichloromethane (50 mL) and was washed with water (2 x 100 mL). Drying (MgSO₄) of the organic phase and concentration *in vacuo* afforded 0.57 g crude product. Purification by

column chromatography on silica gel eluting first with ethyl acetate:heptane (1:1) then with methanol afforded 0.1 g of *the title compound*.

HPLC-MS (Method A): m/z: 346 (M+23); Rt = 2.89 min.

- 5 ¹H-NMR (DMSO-d₆): δ 3.67 (3H, s), 6.62 (1H, d), 6.77 (2H, d), 6.96 (2H, d), 7.40 (1H, dd),
8.05 (1H, d), 9.6 (1H, bs).

General procedure (E) for preparation of compounds of general formula I₄:



10

wherein Lea is a leaving group such as Cl, Br, I or OSO₂CF₃, R is hydrogen or C₁-C₆-alkyl, optionally the two R-groups may together form a 5-8 membered ring, a cyclic boronic acid ester, and J is as defined above.

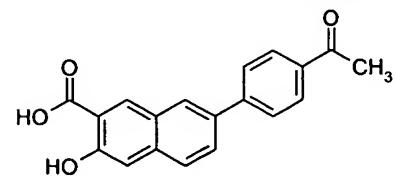
15

An analogous chemical transformation has previously been described in the literature (Bumagin et al., *Tetrahedron*, 1997, 53, 14437-14450). The reaction is generally known as the Suzuki coupling reaction and is generally performed by reacting an aryl halide or triflate with an arylboronic acid or a heteroarylboronic acid in the presence of a palladium catalyst and a base such as sodium acetate, sodium carbonate or sodium hydroxide. The solvent can be water, acetone, DMF, NMP, HMPA, methanol, ethanol toluene or a mixture of two or more of these solvents. The reaction is performed at room temperature or at elevated temperature.

The general procedure (E) is further illustrated in the following example:

- 25 Example 544 (General Procedure (E))

7-(4-Acetylphenyl)-3-hydroxynaphthalene-2-carboxylic Acid



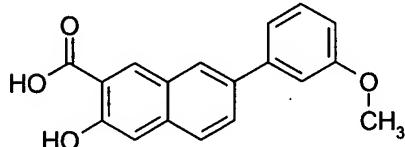
To 7-bromo-3-hydroxynaphthalene-2-carboxylic acid (100 mg, 0.37 mmol) (example 533) was added a solution of 4-acetylphenylboronic acid (92 mg, 0.56 mmol) in acetone (2.2 mL) followed by a solution of sodium carbonate (198 mg, 1.87 mmol) in water (3.3 mL). A suspension of palladium(II) acetate (4 mg, 0.02 mmol) in acetone (0.5 mL) was filtered and 5 added to the above solution. The mixture was purged with N₂ and stirred vigorously for 24 hours at room temperature. The reaction mixture was poured into 1 N hydrochloric acid (aq.) (60 mL) and the precipitate was filtered off and rinsed with water (3 x 40 mL). The crude product was dissolved in acetone (25 mL) and dried with magnesium sulfate (1 h). Filtration followed by concentration furnished the title compound as a solid (92 mg).

10 ¹H-NMR (DMSO-d₆): δ 12.60 (1H, bs), 8.64 (1H, s), 8.42 (1H, s), 8.08 (2H, d), 7.97 (2H, d), 7.92 (2H, m), 7.33 (1H, s), 2.63 (3H, s); HPLC-MS (Method (A)): m/z: 307 (M+1); Rt = 3.84 min.

15 The compounds in the following examples were prepared in a similar fashion. Optionally, the compounds can be further purified by recrystallization from e.g. ethanol or by chromatography.

Example 545 (General Procedure (E))

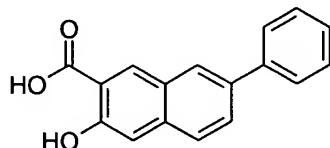
3-Hydroxy-7-(3-methoxyphenyl)naphthalene-2-carboxylic acid



20 HPLC-MS (Method (A)): m/z: 295 (M+1); Rt = 4.60 min.

Example 546 (General Procedure (E))

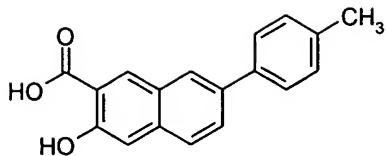
3-Hydroxy-7-phenylnaphthalene-2-carboxylic acid



25 HPLC-MS (Method (A)): m/z: 265 (M+1); Rt = 4.6 min.

Example 547 (General Procedure (E))

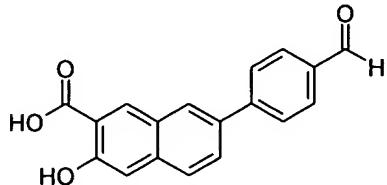
3-Hydroxy-7-p-tolylnaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 279 (M+1); Rt = 4.95 min.

Example 548 (General Procedure (E))

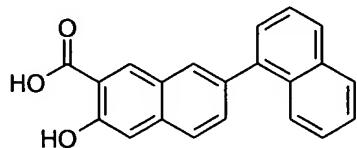
- 5 7-(4-Formylphenyl)-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 293 (M+1); Rt = 4.4 min.

Example 549 (General Procedure (E))

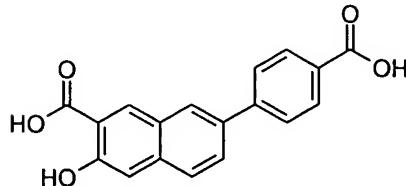
- 10 6-Hydroxy-[1,2]binaphthalenyl-7-carboxylic acid



HPLC-MS (Method (A)): m/z: 315 (M+1); Rt = 5.17 min.

Example 550 (General Procedure (E))

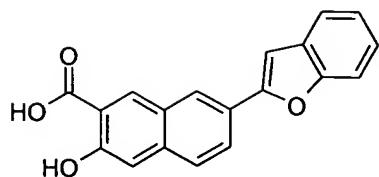
- 15 7-(4-Carboxy-phenyl)-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 309 (M+1); Rt = 3.60 min.

Example 551 (General Procedure (E))

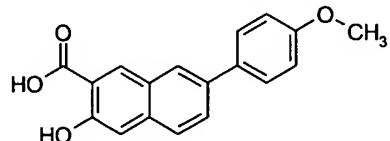
- 20 7-Benzofuran-2-yl-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 305 (M+1); Rt = 4.97 min.

Example 552 (General Procedure (E))

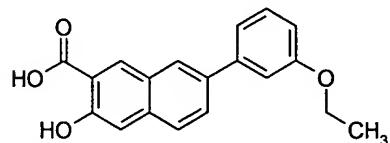
- 5 3-Hydroxy-7-(4-methoxyphenyl)-naphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 295 (M+1); Rt = 4.68 min.

Example 553 (General Procedure (E))

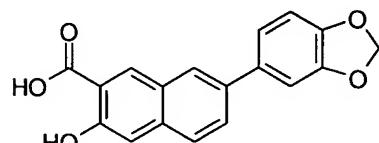
- 10 7-(3-Ethoxyphenyl)-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 309 (M+1); Rt = 4.89 min.

Example 554 (General Procedure (E))

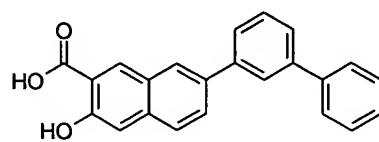
- 15 7-Benzo[1,3]dioxol-5-yl-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 309 (M+1); Rt = 5.61 min.

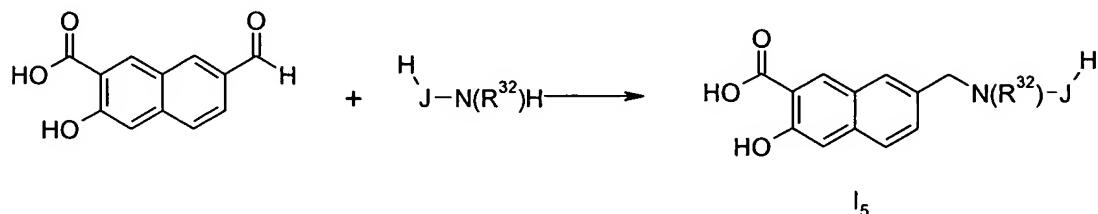
Example 555 (General Procedure (E))

- 20 7-Biphenyl-3-yl-3-hydroxynaphthalene-2-carboxylic acid



HPLC-MS (Method (A)): m/z: 341 (M+1); Rt = 5.45 min.

General procedure (F) for preparation of compounds of general formula I₅:



5

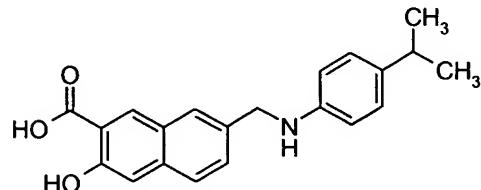
wherein R³⁰ is hydrogen or C₁-C₆-alkyl and T is as defined above

This general procedure (F) is further illustrated in the following example:

10

Example 556 (General procedure (F))

3-Hydroxy-7-[(4-(2-propyl)phenylamino)methyl]naphthalene-2-carboxylic Acid



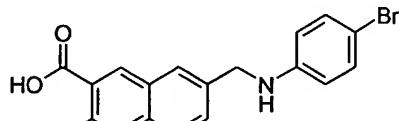
7-Formyl-3-hydroxynaphthalene-2-carboxylic acid (40 mg, 0.19 mmol) (example 535) was suspended in methanol (300 µL). Acetic acid (16 µL, 17 mg, 0.28 mmol) and 4-(2-propyl)aniline (40 µL, 40 mg, 0.30 mmol) were added consecutively, and the resulting mixture was stirred vigorously at room temperature for 2 hours. Sodium cyanoborohydride (1.0 M in tetrahydrofuran, 300 µL, 0.3 mmol) was added, and the stirring was continued for another 17 hours. The reaction mixture was poured into 6 N hydrochloric acid (aq.) (6 mL), and the precipitate was filtered off and rinsed with water (3 x 2 mL) to yield the title compound (40 mg) as its hydrochloride salt. No further purification was necessary.

¹H-NMR (DMSO-d₆): δ 10.95 (1H, bs), 8.45 (1H, s), 7.96 (1H, s), 7.78 (1H, d), 7.62 (1H, d), 7.32 (1H, s), 7.13 (2H, bd), 6.98 (2H, bd), 4.48 (2H, s), 2.79 (1H, sept), 1.14 (6H, d); HPLC-MS (Method (A)): m/z: 336 (M+1); Rt = 3.92 min.

The compounds in the following examples were made using this general procedure (F).

Example 557 (General procedure (F))

7-{[(4-Bromophenyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid

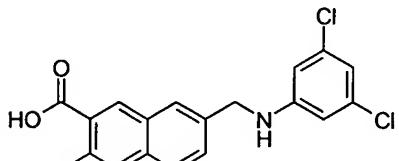


5

HPLC-MS (Method C): m/z: 372 (M+1); Rt = 4.31min.

Example 558 (General procedure (F))

7-{[(3,5-Dichlorophenyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid

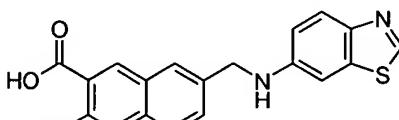


10

HPLC-MS (Method C): m/z: 362 (M+1); Rt = 4.75 min.

Example 559 (General procedure (F))

7-{[(Benzothiazol-6-yl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid

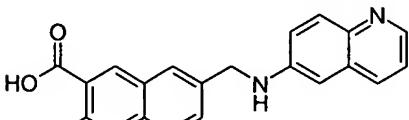


15

HPLC-MS (Method C): m/z: 351 (M+1); Rt = 3.43 min.

Example 560 (General procedure (F))

3-Hydroxy-7-{[(quinolin-6-yl)amino]methyl}naphthalene-2-carboxylic Acid

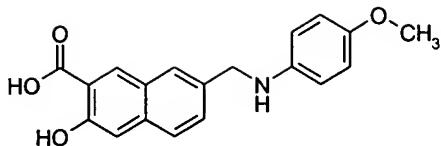


20

HPLC-MS (Method C): m/z: 345 (M+1); Rt = 2.26 min.

Example 561 (General procedure (F))

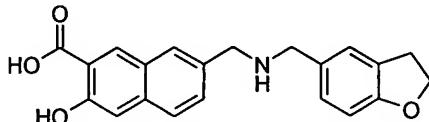
3-Hydroxy-7-{[(4-methoxyphenyl)amino]methyl}naphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 324 (M+1); Rt = 2.57min.

Example 562 (General procedure (F))

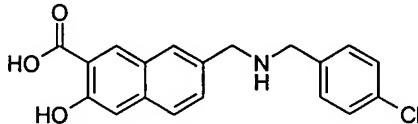
- 5 7-{[(2,3-Dihydrobenzofuran-5-ylmethyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 350 (M+1); Rt = 2.22 min.

- 10 Example 563 (General procedure (F))

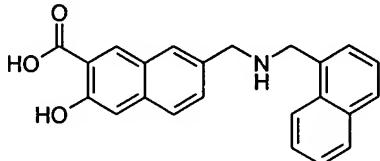
7-{[(4-Chlorobenzyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 342 (M+1); Rt = 2.45 min.

- 15 Example 564 (General procedure (F))

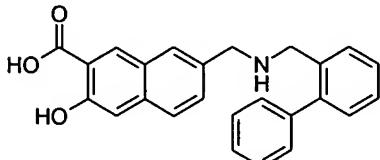
3-Hydroxy-7-{[(naphthalen-1-ylmethyl)amino]methyl}naphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 357 (M+1); Rt = 2.63 min.

- 20 Example 565 (General procedure (F))

7-{[(Biphenyl-2-ylmethyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid

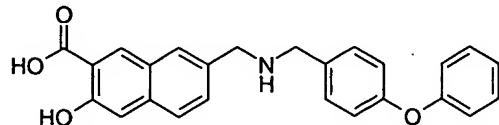


238

HPLC-MS (Method C): m/z: 384 (M+1); Rt = 2.90 min.

Example 566 (General procedure (F))

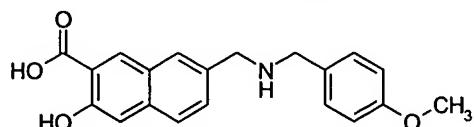
3-Hydroxy-7-{[(4-phenoxybenzyl)amino]methyl}naphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 400 (M+1); Rt = 3.15 min.

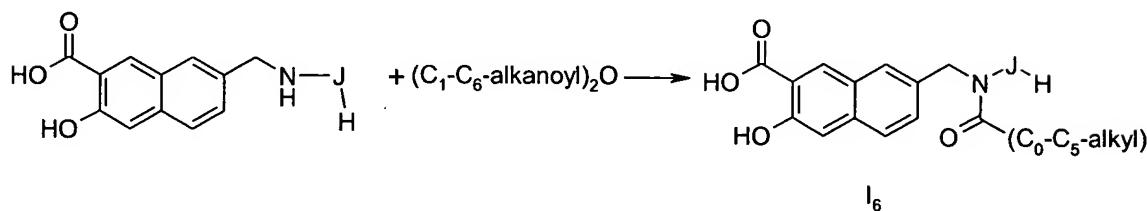
Example 567 (General procedure (F))

3-Hydroxy-7-{[(4-methoxybenzyl)amino]methyl}naphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 338 (M+1); Rt = 2.32 min.

General procedure (G) for preparation of compounds of general formula I₆:

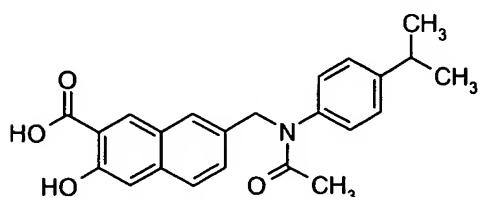


wherein J is as defined above and the moiety (C₁-C₆-alkanoyl)₂O is an anhydride.

The general procedure (G) is illustrated by the following example:

20 **Example 568 (General procedure (G))**

N-Acetyl-3-hydroxy-7-{[(4-(2-propyl)phenylamino)methyl]naphthalene-2-carboxylic Acid



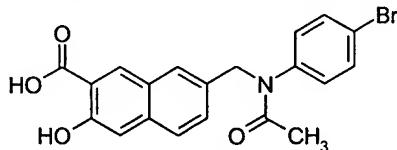
3-Hydroxy-7-[(4-(2-propyl)phenylamino)methyl]naphthalene-2-carboxylic acid (25 mg, 0.07 mmol) (example 556) was suspended in tetrahydrofuran (200 µL). A solution of sodium hydrogencarbonate (23 mg, 0.27 mmol) in water (200 µL) was added followed by acetic anhydride (14 µL, 15 mg, 0.15 mmol). The reaction mixture was stirred vigorously for 65 hours at room temperature before 6 N hydrochloric acid (4 mL) was added. The precipitate was filtered off and rinsed with water (3 x 1 mL) to yield the title compound (21 mg). No further purification was necessary.

¹H-NMR (DMSO-d₆): δ 10.96 (1H, bs), 8.48 (1H, s), 7.73 (1H, s), 7.72 (1H, d), 7.41 (1H, dd), 7.28 (1H, s), 7.23 (2H, d), 7.18 (2H, d), 4.96 (2H, s), 2.85 (1H, sept), 1.86 (3H, s), 1.15 (6H, d); HPLC-MS (Method (A)): m/z: 378 (M+1); Rt = 3.90 min.

The compounds in the following examples were prepared in a similar fashion.

15 Example 569 (General procedure (G))

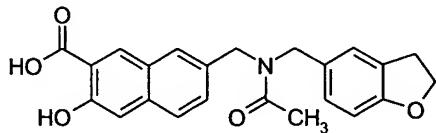
N-Acetyl-7-{[(4-bromophenyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



HPLC-MS (Method C): m/z: 414 (M+1); Rt = 3.76 min.

20 Example 570 (General procedure (G))

N-Acetyl-7-{[(2,3-dihydrobenzofuran-5-ylmethyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid

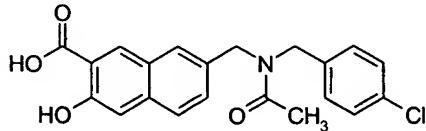


HPLC-MS (Method C): m/z: 392 (M+1); Rt = 3.26 min.

25

Example 571 (General procedure (G))

N-Acetyl-7-{[(4-chlorobenzyl)amino]methyl}-3-hydroxynaphthalene-2-carboxylic Acid



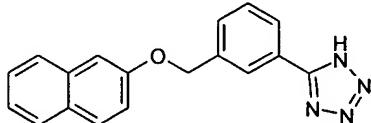
240

HPLC-MS (Method C): m/z: 384 (M+1); Rt = 3.67 min.

Compounds of the invention may also include tetrazoles:

Example 572

- 5 5-(3-(Naphthalen-2-yloxyethyl)-phenyl)-1*H*-tetrazole



To a mixture of 2-naphthol (10 g, 0.07 mol) and potassium carbonate (10 g, 0.073 mol) in acetone (150 mL), alpha-bromo-m-tolunitril (13.6 g, 0.07 mol) was added in portions. The reaction mixture was stirred at reflux temperature for 2.5 hours. The cooled reaction mixture
10 was filtered and evaporated in vacuo affording an oily residue (19 g) which was dissolved in diethyl ether (150 mL) and stirred with a mixture of active carbon and MgSO₄ for 16 hours. The mixture was filtered and evaporated in vacuo affording crude 18.0 g (100 %) of 3-(naphthalen-2-yloxyethyl)-benzonitrile as a solid.
15 12 g of the above benzonitrile was recrystallised from ethanol (150 mL) affording 8.3 g (69 %) of 3-(naphthalen-2-yloxyethyl)-benzonitrile as a solid.

M.p. 60 - 61 °C.

Calculated for C₁₈H₁₃NO:

C, 83.37 %; H, 5.05 %; N, 5.40 %; Found

20 C, 83.51 %; H, 5.03 %; N, 5.38 %.

To a mixture of sodium azide (1.46 g, 22.5 mmol) and ammonium chloride (1.28 g, 24.0 mmol) in dry dimethylformamide (20 mL) under an atmosphere of nitrogen, 3-(naphthalen-2-yloxyethyl)-benzonitrile (3.9 g, 15 mmol) was added and the reaction mixture was stirred at
25 125 °C for 4 hours. The cooled reaction mixture was poured on to ice water (300 mL) and acidified to pH = 1 with 1 N hydrochloric acid. The precipitate was filtered off and washed with water, dried at 100 °C for 4 hours affording 4.2 g (93 %) of the title compound.

M.p. 200 - 202 °C.

30 Calculated for C₁₈H₁₄N₄O:

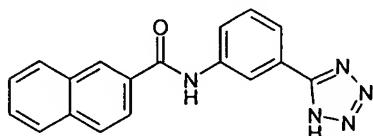
C, 71.51 %; H, 4.67 %; N, 18.54 %; Found

C, 72.11 %; H, 4.65 %; N, 17.43 %.

¹H NMR (400 MHz, DMSO-d₆) δ_H 5.36 (s, 2H), 7.29 (dd, 1H), 7.36 (dt, 1H), 7.47 (m, 2H), 7.66 (t, 1H), 7.74 (d, 1H), 7.84 (m, 3H), 8.02 (d, 1H), 8.22 (s, 1H).

5 Example 573

N-(3-(Tetrazol-5-yl)phenyl)-2-naphtoic acid amide



2-Naphtoic acid (10 g, 58 mmol) was dissolved in dichloromethane (100 mL) and N,N-dimethylformamide (0.2 mL) was added followed by thionyl chloride (5.1 ml, 70 mmol). The mixture was heated at reflux temperature for 2 hours. After cooling to room temperature, the mixture was added dropwise to a mixture of 3-aminobenzonitril (6.90 g, 58 mmol) and triethylamine (10 mL) in dichloromethane (75 mL). The resulting mixture was stirred at room temperature for 30 minutes. Water (50 mL) was added and the volatiles were evaporated in vacuo. The resulting mixture was filtered and the filter cake was washed with water followed by heptane (2 x 25 mL). Drying in vacuo at 50 °C for 16 hours afforded 15.0 g (95 %) of N-(3-cyanophenyl)-2-naphtoic acid amide.

M.p. 138-140 °C

20 The above naphthoic acid amide (10 g, 37 mmol) was dissolved in N,N-dimethylformamide (200 mL) and sodium azide (2.63 g, 40 mmol) and ammonium chloride (2.16 g, 40 mmol) were added and the mixture heated at 125 °C for 6 hours. Sodium azide (1.2 g) and ammonium chloride (0.98 g) were added and the mixture heated at 125 °C for 16 hours. After 25 cooling, the mixture was poured into water (1.5 l) and stirred at room temperature for 30 minutes. The solid formed was filtered off, washed with water and dried in vacuo at 50 °C for 3 days affording 9.69 g (84 %) of the title compound as a solid which could be further purified by treatment with ethanol at reflux temperature.

30 ¹H NMR (200 MHz, DMSO-d₆): δ_H 7.58-7.70 (m, 3H), 7.77 (d, 1H), 8.04-8.13 (m, 5H), 8.65 (d, 1H), 10.7 (s, 1H).

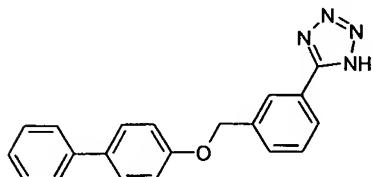
Calculated for C₁₈H₁₃N₅O, 0.75 H₂O:

C, 65.74 %; H, 4.44 %; N, 21.30 %. Found:

C, 65.58 %; H, 4.50 %; N, 21.05 %.

5 Example 574

5-[3-(Biphenyl-4-yloxymethyl)phenyl]-1*H*-tetrazole



To a solution of 4-phenylphenol (10.0 g, 59 mmol) in dry N,N-dimethyl-formamide (45 mL) kept under an atmosphere of nitrogen, sodium hydride (2.82 g, 71 mmol, 60 % dispersion in oil) was added in portions and the reaction mixture was stirred until gas evolution ceased. A solution of m-cyanobenzyl bromide (13 g, 65 mmol) in dry N,N-dimethylformamide (45 mL) was added dropwise and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was poured on to ice water (150 mL). The precipitate was filtered off and washed with 50 % ethanol

15 (3 x 50 mL), ethanol (2 x 50 mL), diethyl ether (80 mL), and dried in vacuo at 50 °C for 18 hours affording crude 17.39 g of 3-(biphenyl-4-yloxymethyl)-benzonitrile as a solid.

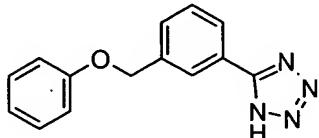
¹H NMR (200 MHz, CDCl₃) δ_H 5.14 (s, 2H), 7.05 (m, 2H), 7.30 - 7.78 (m, 11H).

20 To a mixture of sodium azide (2.96 g, 45.6 mmol) and ammonium chloride (2.44 g, 45.6 mmol) in dry N,N-dimethylformamide (100 mL) under an atmosphere of nitrogen, 3-(biphenyl-4-yloxymethyl)-benzonitrile (10.0 g, 35.0 mmol) was added and the reaction mixture was stirred at 125 °C for 18 hours. The cooled reaction mixture was poured on to a mixture of 1N hydrochloric acid (60 mL) and ice water (500 mL). The precipitate was filtered off and washed with water (3 x 100 mL), 50 % ethanol (3 x 100 mL), ethanol (50 mL), diethyl ether (50 mL), ethanol (80 mL), and dried in vacuo at 50 °C for 18 hours affording 8.02 g (70 %) of the title compound.

30 ¹H NMR (200 MHz, DMSO-d₆) δ_H 5.31 (s, 2H), 7.19 (m, 2H), 7.34 (m, 1H), 7.47 (m, 2H), 7.69 (m, 6H), 8.05 (dt, 1H), 8.24 (s, 1H).

Example 575

5-(3-Phenoxyethyl)-phenyl-tetrazole



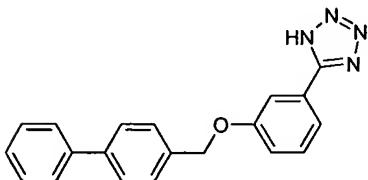
- 5 3-Bromomethylbenzonitrile (5.00 g, 25.5 mmol) was dissolved in N,N-dimethylformamide (50 mL), phenol (2.40 g, 25.5 mmol) and potassium carbonate (10.6 g, 77 mmol) were added. The mixture was stirred at room temperature for 16 hours. The mixture was poured into water (400 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with water (2 x 100 mL), dried (MgSO_4) and evaporated in vacuo to afford 5.19 g (97 %) 3-(phenoxyethyl)benzonitrile as an oil.
- 10 TLC: R_f = 0.38 (Ethyl acetate/heptane = 1:4)

- 15 The above benzonitrile (5.19 g, 24.8 mmol) was dissolved in N,N-dimethylformamide (100 mL) and sodium azide (1.93 g, 30 mmol) and ammonium chloride (1.59 g, 30 mmol) were added and the mixture was heated at 140 °C for 16 hours. After cooling, the mixture was poured into water (800 mL). The aqueous mixture was washed with ethyl acetate (200 mL). The pH of the aqueous phase was adjusted to 1 with 5 N hydrochloric acid and stirred at room temperature for 30 minutes. Filtration, washing with water and drying in vacuo at 50 °C afforded 2.06 g (33 %) of the title compound as a solid.

^1H NMR (200 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$) δ_{H} 5.05 (s, 2H), 6.88 (m, 3H), 7.21 (m, 2H), 7.51 (m, 2H), 7.96 (dt, 1H), 8.14 (s, 1H).

Example 576

25 5-[3-(Biphenyl-4-ylmethoxy)phenyl]-1H-tetrazole



To a solution of 3-cyanophenol (5.0 g, 40.72 mmol) in dry N,N-dimethylformamide (100 mL) kept under an atmosphere of nitrogen, sodium hydride (2 g, 48.86 mmol, 60 % dispersion in oil) was added in portions and the reaction mixture was stirred until gas evolution ceased. p-

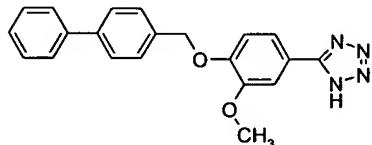
Phenylbenzyl chloride (9.26 g, 44.79 mmol) and potassium iodide (0.2 g, 1.21 mmol) were added and the reaction mixture was stirred at room temperature for 60 hours. The reaction mixture was poured on to a mixture of saturated sodium carbonate (100 mL) and ice water (300 mL). The precipitate was filtered off and washed with water (3 x 100 mL), n-hexane (2 x 5 mL) and dried in vacuo at 50 °C for 18 hours affording 11.34 g (98 %) of 3-(biphenyl-4-ylmethoxy)-benzonitrile as a solid.

To a mixture of sodium azide (2.37 g, 36.45 mmol) and ammonium chloride (1.95 g, 36.45 mmol) in dry N,N-dimethylformamide (100 mL) under an atmosphere of nitrogen, 3-(biphenyl-4-ylmethoxy)-benzonitrile (8.0 g, 28.04 mmol) was added and the reaction mixture was stirred at 125 °C for 18 hours. To the cooled reaction mixture water (100 mL) was added and the reaction mixture stirred for 0.75 hour. The precipitate was filtered off and washed with water, 96 % ethanol (2 x 50 mL), and dried in vacuo at 50°C for 18 hours affording 5.13 g (56 %) of the title compound.

¹H NMR (200 MHz, DMSO-d₆) δ_H 5.29 (s, 2H), 7.31 (dd, 1H), 7.37 - 7.77 (m, 12H).

Example 577

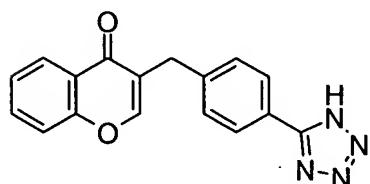
20 5-[4-(Biphenyl-4-ylmethoxy)-3-methoxyphenyl]-1H-tetrazol



This compound was made similarly as described in example 576.

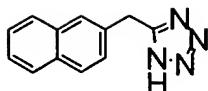
Example 578

25



Example 579

5-(2-Naphthylmethyl)-1H-tetrazole



This compound was prepared similarly as described in example 572, step 2.

Example 580

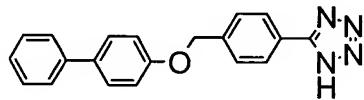
- 5 5-(1-Naphthylmethyl)-1H-tetrazole



This compound was prepared similarly as described in example 572, step 2.

Example 581

- 10 5-[4-(Biphenyl-4-yloxy)methyl]phenyl]-1H-tetrazole



A solution of alpha-bromo-p-tolunitrile (5.00 g, 25.5 mmol), 4-phenylphenol (4.56 g, 26.8 mmol), and potassium carbonate (10.6 g, 76.5 mmol) in N,N-dimethylformamide (75 mL) was stirred vigorously for 16 hours at room temperature. Water (75 mL) was added and the

- 15 mixture was stirred at room temperature for 1 hour. The precipitate was filtered off and washed with thoroughly with water. Drying in vacuo over night at 50 °C afforded 7.09 g (97 %) of 4-(biphenyl-4-yloxy)methylbenzonitrile as a solid.

The above benzonitrile (3.00 g, 10.5 mmol) was dissolved in N,N-dimethylformamide (50

- 20 mL), and sodium azide (1.03 g, 15.8 mmol) and ammonium chloride (0.84 g, 15.8 mmol) were added and the mixture was stirred 16 hours at 125 °C. The mixture was cooled to room temperature and water (50 mL) was added. The suspension was stirred overnight, filtered, washed with water and dried in vacuo at 50 °C for 3 days to give crude 3.07 g (89 %) of the title compound. From the mother liquor crystals were collected and washed with water, dried
25 by suction to give 0.18 g
(5 %) of the title compound as a solid.

246

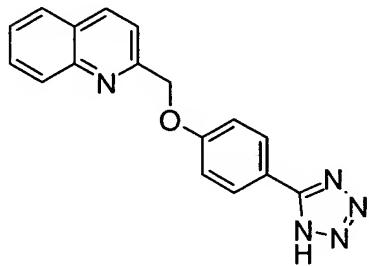
¹H NMR (200 MHz, DMSO-d₆): δ_H 5.21 (s, 2H), 7.12 (d, 2H), 7.30 (t, 1H), 7.42 (t, 2H), 7.56-7.63 (m, 6H), 8.03 (d, 2H).

Calculated for C₂₀H₁₆N₄O, 2H₂O:

5 C, 65.92 %; H, 5.53 %; N, 15.37 %. Found:
C, 65.65 %; H, 5.01 %; N, 14.92 %.

Example 582

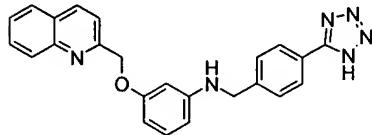
10



This compound was prepared similarly as described in example 576.

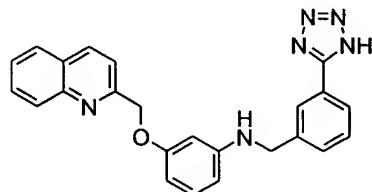
Example 583

15

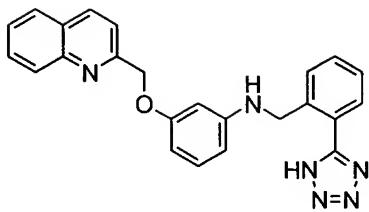
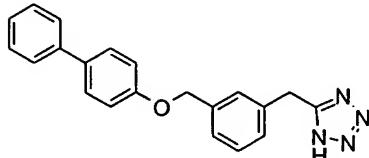


Example 584

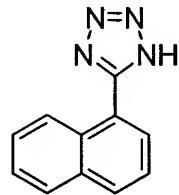
20



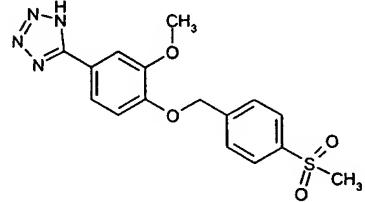
Example 585

**Example 586****5-(3-(Biphenyl-4-yloxymethyl)-benzyl)-1*H*-tetrazole**

5

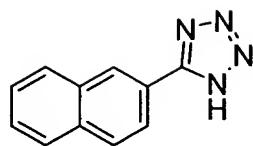
Example 587**5-(1-Naphthyl)-1*H*-tetrazole**

- 10 This compound was prepared similarly as described in example 572, step 2.

Example 588**5-[3-Methoxy-4-(4-methylsulfonylbenzyloxy)phenyl]-1*H*-tetrazole**

- 15 This compound was made similarly as described in example 576.

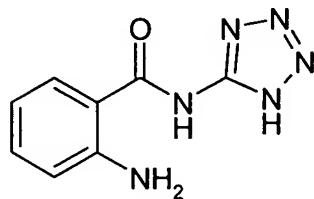
Example 589**5-(2-Naphthyl)-1*H*-tetrazole**



This compound was prepared similarly as described in example 572, step 2.

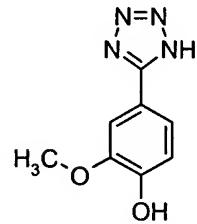
Example 590

- 5 2-Amino-N-(1*H*-tetrazol-5-yl)-benzamide



Example 591

- 5-(4-Hydroxy-3-methoxyphenyl)-1*H*-tetrazole

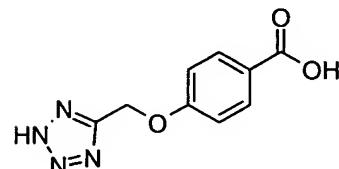


10

This compound was prepared similarly as described in example 572, step 2.

Example 592

- 4-(2*H*-Tetrazol-5-ylmethoxy)benzoic acid



15

To a mixture of methyl 4-hydroxybenzoate (30.0 g, 0.20 mol), sodium iodide (30.0 g, 0.20 mol) and potassium carbonate (27.6 g, 0.20 mol) in acetone (2000 mL) was added chloroacetonitrile (14.9 g, 0.20 mol). The mixture was stirred at RT for 3 days. Water was added and the mixture was acidified with 1N hydrochloric acid and the mixture was extracted with diethyl ether. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was dissolved in acetone and chloroacetonitrile (6.04 g, 0.08 mol),

sodium iodide (12.0 g, 0.08 mol) and potassium carbonate (11.1 g, 0.08 mol) were added and the mixture was stirred for 16 hours at RT and at 60 °C. More chloroacetonitrile was added until the conversion was 97%. Water was added and the mixture was acidified with 1N hydrochloric acid and the mixture was extracted with diethyl ether. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo* to afford methyl 4-cyanomethoxybenzoate in quantitative yield. This compound was used without further purification in the following step.

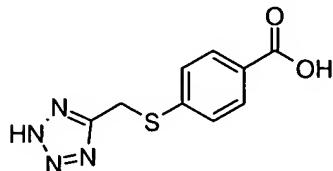
A mixture of methyl 4-cyanomethoxybenzoate (53.5 g, 0.20 mol), sodium azide (16.9 g, 0.26 mol) and ammonium chloride (13.9 g, 0.26 mol) in DMF 1000 (mL) was refluxed overnight under N₂. After cooling, the mixture was concentrated *in vacuo*. The residue was suspended in cold water and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*, to afford methyl 4-(2*H*-tetrazol-5-ylmethoxy)benzoate. This compound was used as such in the following step.

Methyl 4-(2*H*-Tetrazol-5-ylmethoxy)-benzoate was refluxed in 3N sodium hydroxide. The reaction was followed by TLC (DCM:MeOH = 9:1). The reaction mixture was cooled, acidified and the product filtered off. The impure product was washed with DCM, dissolved in MeOH, filtered and purified by column chromatography on silica gel (DCM:MeOH = 9:1). The resulting product was recrystallised from DCM:MeOH=95:5. This was repeated until the product was pure. This afforded 13.82 g (30 %) of the title compound.

¹H-NMR (DMSO-d₆): 4.70 (2H, s), 7.48 (2H, d), 7.73 (2H, d), 13 (1H, bs).

25 Example 593

4-(2*H*-Tetrazol-5-ylmethylsulfanyl)benzoic acid



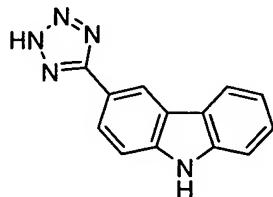
To a solution of sodium hydroxide (10.4 g, 0.26 mol) in degassed water (600 mL) was added 4-mercaptopbenzoic acid (20.0 g, 0.13 mol). This solution was stirred for 30 minutes. To a solution of potassium carbonate (9.0 g, 65 mmol) in degassed water (400 mL) was added chloroacetonitrile (9.8 g, (0.13 mol) portion-wise. These two solutions were mixed and stirred for 48 hours at RT under N₂. The mixture was filtered and washed with heptane. The

aqueous phase was acidified with 3N hydrochloric acid and the product was filtered off, washed with water and dried, affording 4-cyanomethylsulfanylbenzoic acid (27.2 g, 88%). This compound was used without further purification in the following step.

- 5 A mixture of 4-cyanomethylsulfanylbenzoic acid (27.2 g, 0.14 mol), sodium azide (11.8 g, 0.18 mol) and ammonium chloride (9.7 g, 0.18 mol) in DMF (1000 mL) was refluxed overnight under N₂. The mixture was concentrated *in vacuo*. The residue was suspended in cold water and extracted with diethyl ether. The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Water was added and the precipitate
- 10 was filtered off. The aqueous layer was concentrated *in vacuo*, water was added and the precipitate filtered off. The combined impure products were purified by column chromatography using DCM:MeOH = 9:1 as eluent, affording the title compound (5.2 g, 16%).
- 15 ¹H-NMR (DMSO-d₆): 5.58 (2H, s), 7.15 (2H, d), 7.93 (2H, d), 12.7 (1H, bs).

Example 594

3-(2*H*-Tetrazol-5-yl)-9*H*-carbazole



- 20 3-Bromo-9*H*-carbazole was prepared as described by Smith *et al.* in *Tetrahedron* **1992**, *48*, 7479-7488.
A solution of 3-bromo-9*H*-carbazole (23.08 g, 0.094 mol) and cuprous cyanide (9.33 g, 0.103 mol) in *N*-methyl-pyrrolidone (300 ml) was heated at 200 °C for 5 h. The cooled reaction mixture was poured on to water (600 ml) and the precipitate was filtered off and washed with
- 25 ethyl acetate (3 x 50 ml). The filtrate was extracted with ethyl acetate (3 x 250 ml) and the combined ethyl acetate extracts were washed with water (150 ml), brine (150 ml), dried (MgSO₄) and concentrated *in vacuo*. The residue was crystallised from heptanes and recrystallised from acetonitrile (70 ml) affording 7.16 g (40 %) of 3-cyano-9*H*-carbazole as a solid. M.p. 180 - 181 °C.

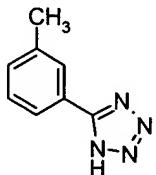
3-Cyano-9*H*-carbazole (5.77 g, 30 mmol) was dissolved in *N,N*-dimethylformamide (150 ml), and sodium azide (9.85 g, 152 mmol), ammonium chloride (8.04 g, 150 mmol) and lithium chloride (1.93 g, 46 mmol) were added and the mixture was stirred for 20 h at 125 °C. To the reaction mixture was added an additional portion of sodium azide (9.85 g, 152 mmol) and 5 ammonium chloride (8.04 g, 150 mmol) and the reaction mixture was stirred for an additional 24 h at 125 °C. The cooled reaction mixture was poured on to water (500 ml). The suspension was stirred for 0.5 h, and the precipitate was filtered off and washed with water (3 x 200 ml) and dried *in vacuo* at 50 °C. The dried crude product was suspended in diethyl ether (500 ml) and stirred for 2 h, filtered off and washed with diethyl ether (2 x 200 ml) and 10 dried *in vacuo* at 50 °C affording 5.79 g (82 %) of the title compound as a solid.

¹H-NMR (DMSO-*d*₆): δ 11.78 (1H, bs), 8.93 (1H, d), 8.23 (1H, d), 8.14 (1H, dd), 7.72 (1H, d), 7.60 (1H, d), 7.49 (1H, t), 7.28 (1H, t); HPLC-MS (Method C): m/z: 236 (M+1); Rt = 2.77 min.

- 15 The following commercially available tetrazoles do all bind to the His B10 Zn²⁺ site of the insulin hexamer:

Example 595

5-(3-Tolyl)-1*H*-tetrazole



20

Example 596

5-(2-Bromophenyl)tetrazole

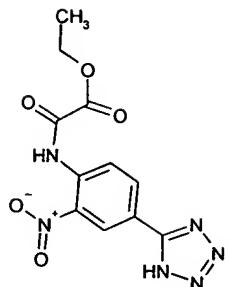


25

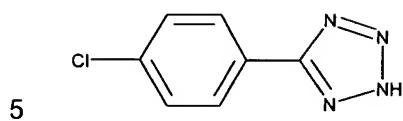
Example 597

5-(4-Ethoxalylamino-3-nitrophenyl)tetrazole

252

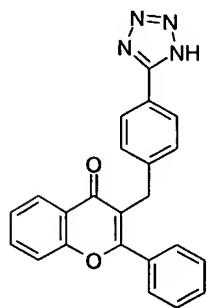


Example 598



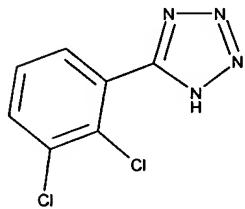
5

Example 599



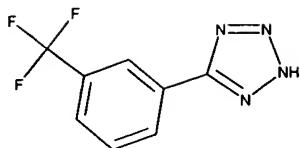
10

Example 600



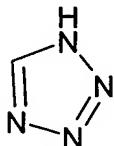
15 Example 601

253



Example 602

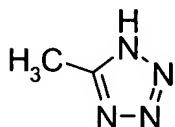
Tetrazole



5

Example 603

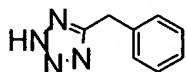
5-Methyltetrazole



10

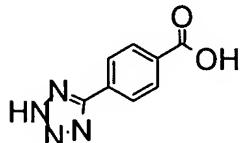
Example 604

5-Benzyl-2H-tetrazole



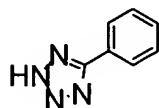
15 Example 605

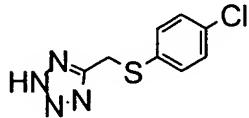
4-(2H-Tetrazol-5-yl)benzoic acid



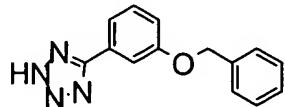
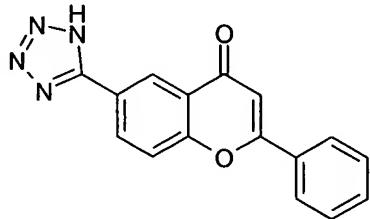
Example 606

20 5-Phenyl-2H-tetrazole

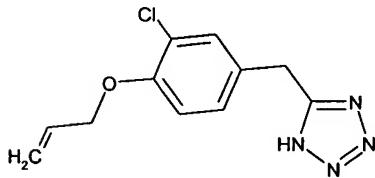


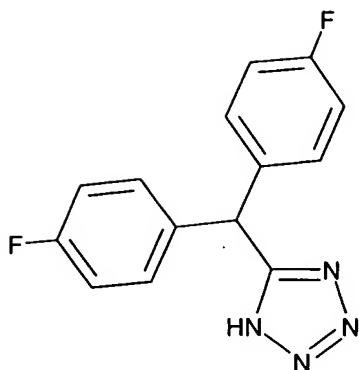
Example 607**5-(4-Chlorophenylsulfanylmethyl)-2H-tetrazole**

5

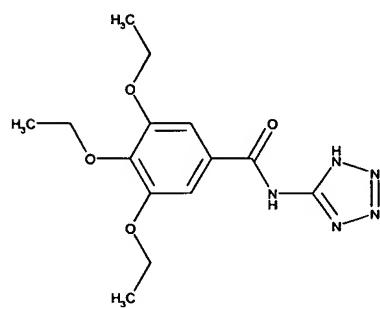
Example 608**5-(3-Benzyloxyphenyl)-2H-tetrazole**10 **Example 609****2-Phenyl-6-(1H-tetrazol-5-yl)-chromen-4-one****Example 610**

15

**Example 611**

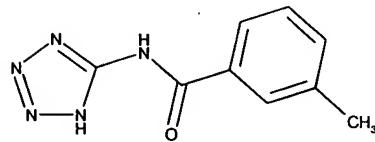


Example 612



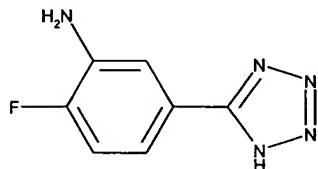
5

Example 613



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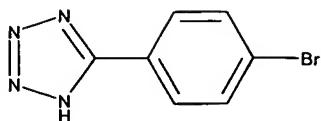
Example 614



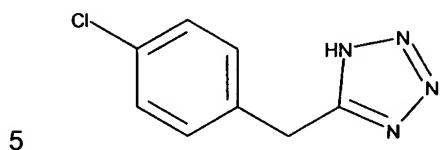
15 Example 615

5-(4-Bromo-phenyl)-1H-tetrazole

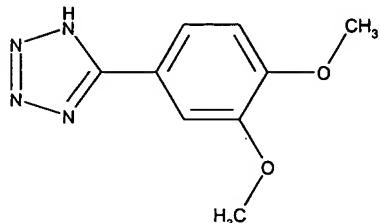
256



Example 616

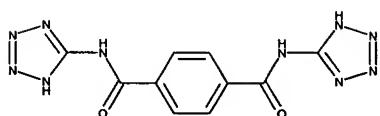


Example 617

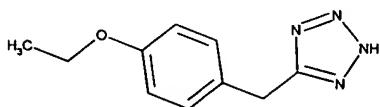


10

Example 618



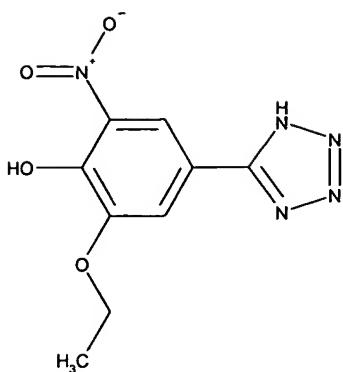
15 Example 619



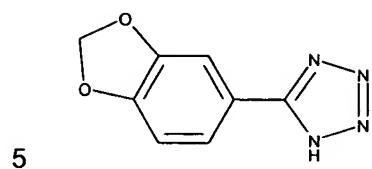
Example 620

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257

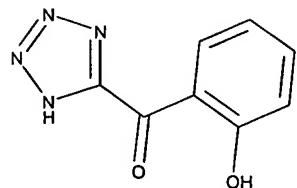


Example 621



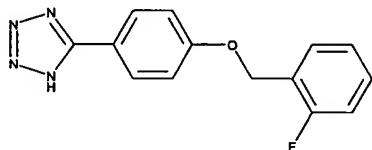
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Example 622



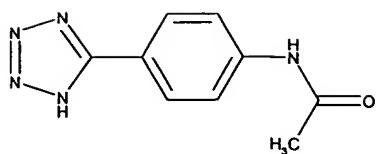
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Example 623

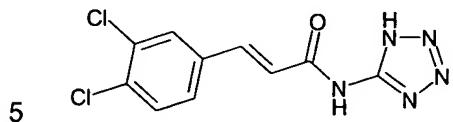


15 Example 624

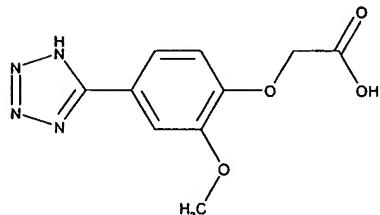
258



Example 625

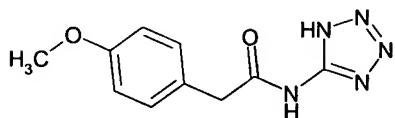


Example 626

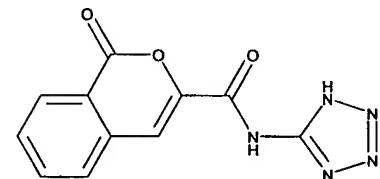


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Example 627



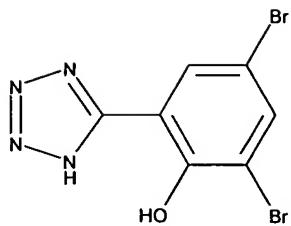
15 Example 628



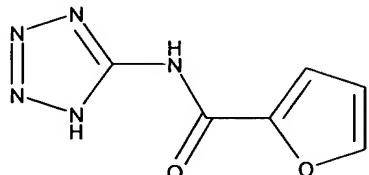
Example 629

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259

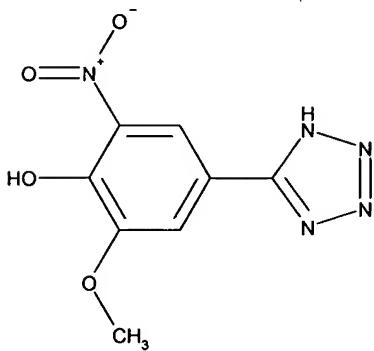


Example 630



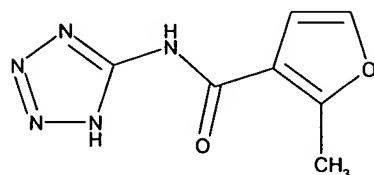
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Example 631



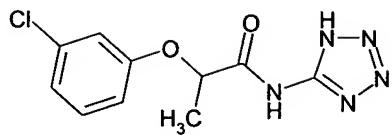
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Example 632

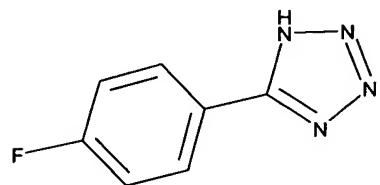


15 Example 633

260

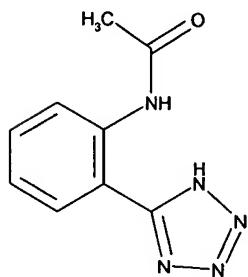


Example 634



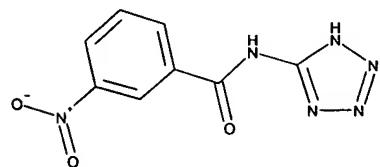
5

Example 635

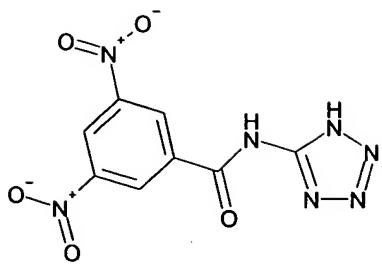


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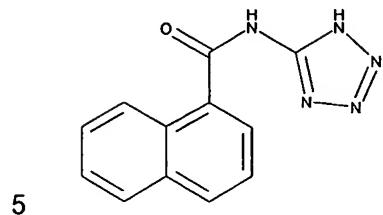
Example 636



15 Example 637

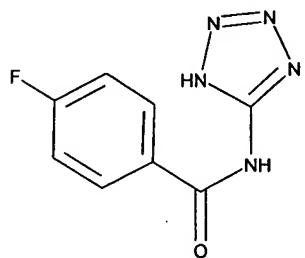


Example 638



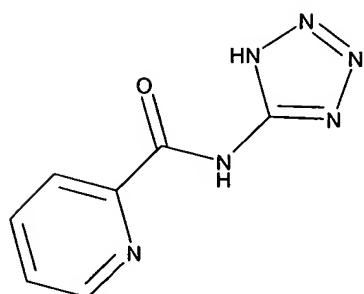
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Example 639



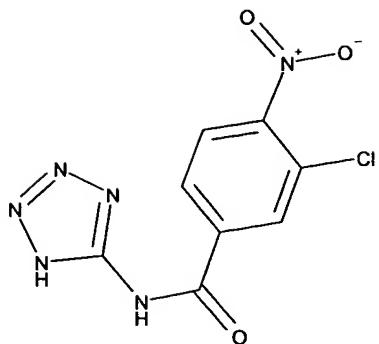
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Example 640

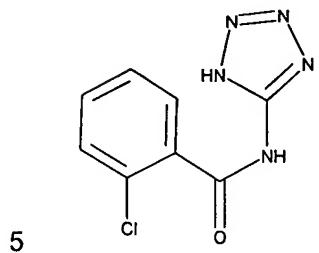


15 Example 641

262

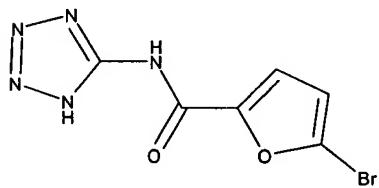


Example 642



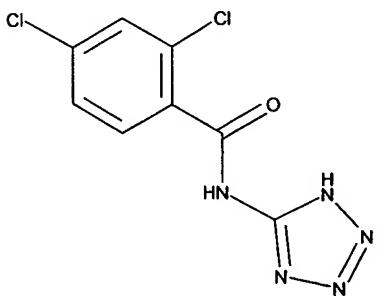
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Example 643

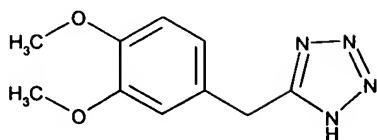


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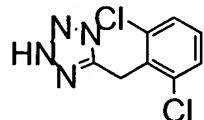
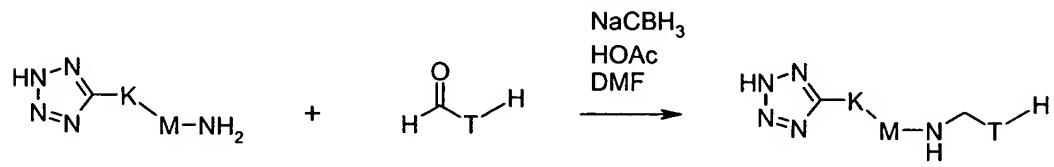
Example 644



Example 645



5 Example 646

5-(2,6-Dichlorobenzyl)-2*H*-tetrazole**General procedure (H) for preparation of compounds of general formula I₇:**

10

wherein K, M, and T are as defined above.

The reaction is generally known as a reductive alkylation reaction and is generally performed by stirring an aldehyde with an amine at low pH (by addition of an acid, such as acetic acid or 15 formic acid) in a solvent such as THF, DMF, NMP, methanol, ethanol, DMSO, dichloromethane, 1,2-dichloroethane, trimethyl orthoformate, triethyl orthoformate, or a mixture of two or more of these. As reducing agent sodium cyano borohydride or sodium triacetoxy borohydride may be used. The reaction is performed between 20°C and 120°C, preferably at room temperature.

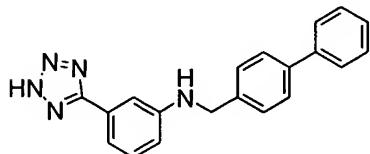
20

When the reductive alkylation is complete, the product is isolated by extraction, filtration, chromatography or other methods known to those skilled in the art.

The general procedure (H) is further illustrated in the following example 647:

25

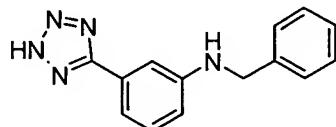
Example 647 (General procedure (H))

Biphenyl-4-ylmethyl-[3-(2*H*-tetrazol-5-yl)phenyl]amine

A solution of 5-(3-aminophenyl)-2*H*-tetrazole (example 874, 48 mg, 0.3 mmol) in DMF (250 µL) was mixed with a solution of 4-biphenylcarbaldehyde (54 mg, 0.3 mmol) in DMF (250 µL) and acetic acid glacial (250 µL) was added to the mixture followed by a solution of sodium cyano borohydride (15 mg, 0.24 mmol) in methanol (250 µL). The resulting mixture was shaken at room temperature for 2 hours. Water (2 mL) was added to the mixture and the resulting mixture was shaken at room temperature for 16 hours. The mixture was centrifuged (6000 rpm, 10 minutes) and the supernatant was removed by a pipette. The residue was washed with water (3 mL), centrifuged (6000 rpm, 10 minutes) and the supernatant was removed by a pipette. The residue was dried *in vacuo* at 40 °C for 16 hours to afford the title compound as a solid.

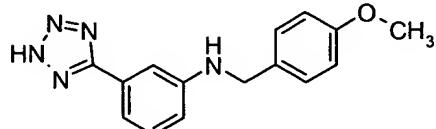
15 HPLC-MS (Method C): m/z: 328 (M+1), 350 (M+23); Rt = 4.09 min.

Example 648 (General procedure (H))

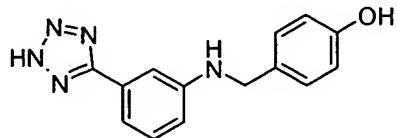
Benzyl-[3-(2*H*-tetrazol-5-yl)phenyl]amine

20 HPLC-MS (Method D): m/z: 252 (M+1); Rt = 3,74 min.

Example 649 (General procedure (H))

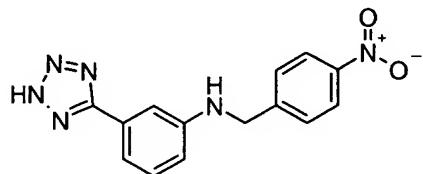
(4-Methoxybenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine

25 HPLC-MS (Method D): m/z: 282,2 (M+1); Rt = 3,57min.

Example 650 (General procedure (H))**4-{{[3-(2*H*-Tetrazol-5-yl)phenylamino]methyl}phenol}**

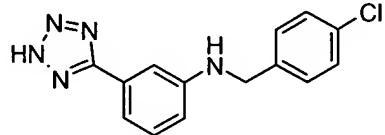
HPLC-MS (Method D): m/z: 268,4 (M+1); Rt = 2,64 min.

5

Example 651 (General procedure (H))**(4-Nitrobenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine**

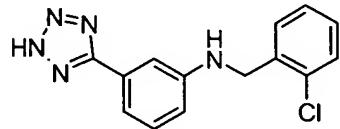
HPLC-MS (Method D): m/z: 297,4 (M+1); Rt = 3,94 min.

10

Example 652 (General procedure (H))**(4-Chlorobenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine**

HPLC-MS (Method D): m/z: 287,2 (M+1); Rt = 4,30 min.

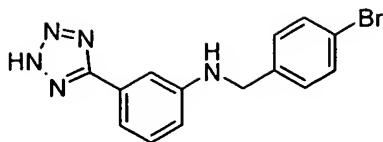
15

Example 653 (General procedure (H))**(2-Chlorobenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine**

HPLC-MS (Method D): m/z: 286 (M+1); Rt = 4,40 min.

20

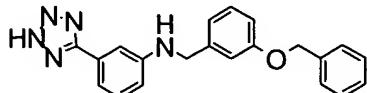
Example 654 (General procedure (H))**(4-Bromobenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine**



HPLC-MS (Method D): m/z:332 (M+1); Rt = 4,50 min.

Example 655 (General procedure (H))

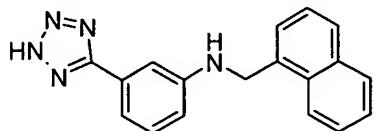
- 5 (3-Benzylxoybenzyl)-[3-(2H-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 4,94 min.

Example 656 (General procedure (H))

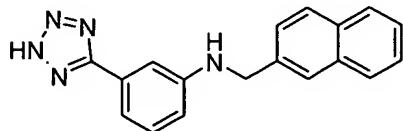
- 10 Naphthalen-1-ylmethyl-[3-(2H-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 302 (M+1); Rt = 4,70 min.

Example 657 (General procedure (H))

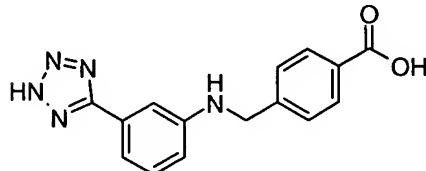
- 15 Naphthalen-2-ylmethyl-[3-(2H-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 302 (M+1); Rt = 4,60 min.

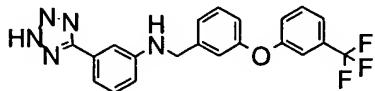
Example 658 (General procedure (H))

- 20 4-{[3-(2H-Tetrazol-5-yl)phenylamino]methyl}benzoic acid



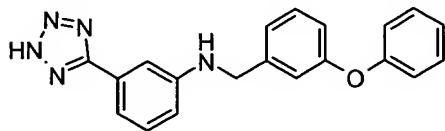
HPLC-MS (Method D): m/z: 296 (M+1); Rt = 3,24 min.

Example 659 (General procedure (H))

(3-(2*H*-Tetrazol-5-yl)-phenyl)-[3-(3-trifluoromethyl-phenoxy)benzyl]amine

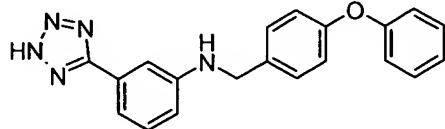
- 5 HPLC-MS (Method D): m/z: 412 (M+1); Rt = 5,54 min.

Example 660 (General procedure (H))

(3-Phenoxybenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine

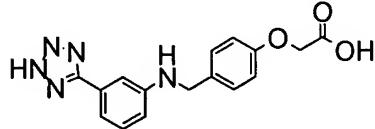
- 10 HPLC-MS (Method D): m/z: 344 (M+1); Rt = 5,04 min.

Example 661 (General procedure (H))

(4-Phenoxy-benzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine

- 15 HPLC-MS (Method D): m/z: 344 (M+1); Rt = 5,00 min.

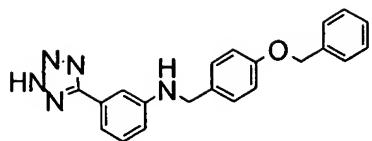
Example 662 (General procedure (H))

(4-[{3-(2*H*-Tetrazol-5-yl)phenylamino}methyl]phenoxy)acetic acid

- 20 HPLC-MS (Method D): m/z: 326 (M+1); Rt = 3,10 min.

Example 663 (General procedure (H))

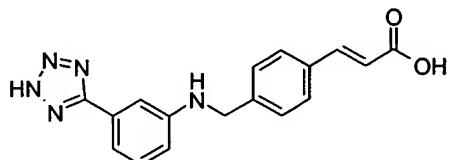
(4-Benzylphenoxybenzyl)-[3-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 4,97 min.

Example 664 (General procedure (H))

- 5 3-(4-{[3-(2H-Tetrazol-5-yl)phenylamino]methyl}phenyl)acrylic acid



HPLC-MS (Method D): m/z: 322 (M+1); Rt = 3,60 min.

Example 665 (General procedure (H))

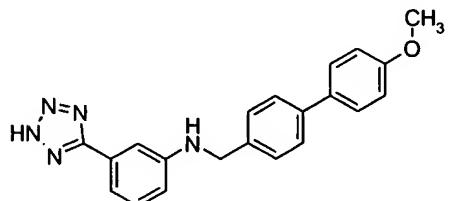
- 10 Dimethyl-(4-{[3-(2H-tetrazol-5-yl)phenylamino]methyl}naphthalen-1-yl)amine



HPLC-MS (Method D): m/z: 345 (M+1); Rt = 3,07 min.

Example 666 (General procedure (H))

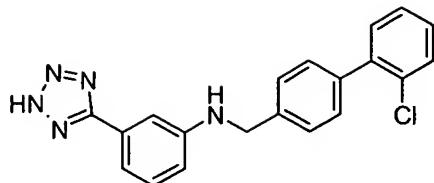
- 15 (4'-Methoxybiphenyl-4-ylmethyl)-[3-(2H-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 4,97 min.

Example 667 (General procedure (H))

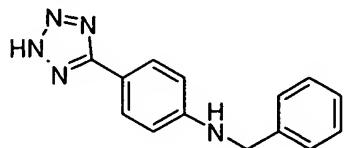
- 20 (2'-Chlorobiphenyl-4-ylmethyl)-[3-(2H-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 362 (M+1); Rt = 5,27 min.

Example 668 (General procedure (H))

- 5 Benzyl-[4-(2*H*-tetrazol-5-yl)phenyl]amine

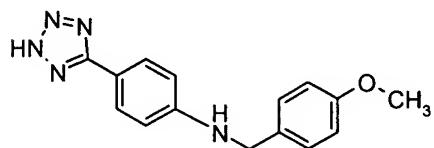


For preparation of starting material, see example 875.

HPLC-MS (Method D): m/z: 252 (M+1); Rt = 3,97 min.

- 10 Example 669 (General procedure (H))

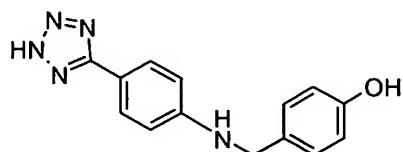
(4-Methoxybenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 282 (M+1); Rt = 3,94 min.

- 15 Example 670 (General procedure (H))

4-{[4-(2*H*-Tetrazol-5-yl)phenylamino]methyl}phenol

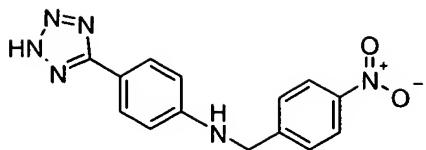


HPLC-MS (Method D): m/z: 268 (M+1); Rt = 3,14 min.

- 20 Example 671 (General procedure (H))

(4-Nitrobenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine

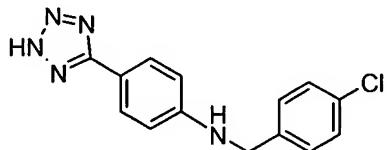
270



HPLC-MS (Method D): m/z: (M+1); Rt = 3,94 min.

Example 672 (General procedure (H))

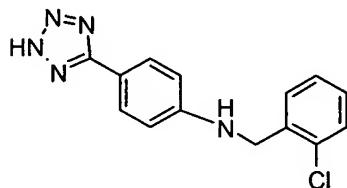
- 5 (4-Chlorobenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: (M+1); Rt = 4,47 min.

Example 673 (General procedure (H))

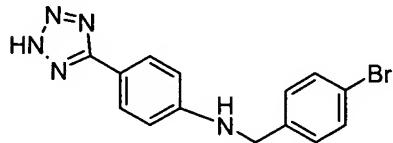
- 10 (2-Chlorobenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 286 (M+1); Rt = 4,37 min.

Example 674 (General procedure (H))

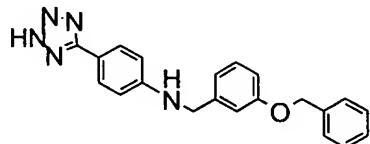
- 15 (4-Bromobenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 331 (M+1); Rt = 4,57 min.

Example 675 (General procedure (H))

- 20 (3-Benzylbenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine

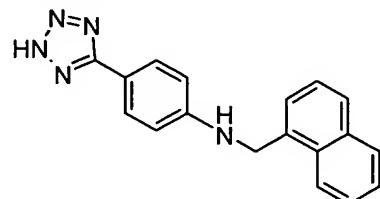


271

HPLC-MS (Method D): m/z: 358 (M+1); Rt = 5,07min.

Example 676 (General procedure (H))

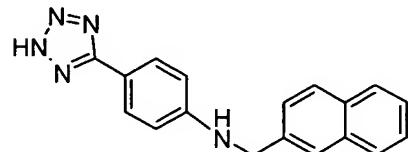
Naphthalen-1-ylmethyl-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 302 (M+1); Rt = 4,70 min.

Example 677 (General procedure (H))

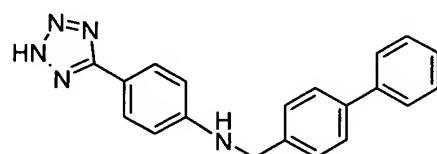
Naphthalen-2-ylmethyl-[4-(2*H*-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 302 (M+1); Rt = 4,70 min.

Example 678 (General procedure (H))

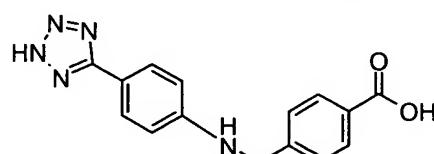
Biphenyl-4-ylmethyl-[4-(2*H*-tetrazol-5-yl)phenyl]amine



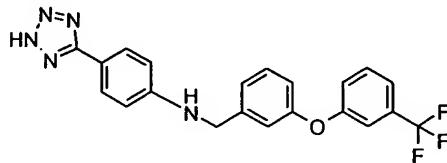
HPLC-MS (Method D): m/z: 328 (M+1); Rt = 5,07 min.

Example 679 (General procedure (H))

4-{[4-(2*H*-Tetrazol-5-yl)phenylamino]methyl}benzoic acid

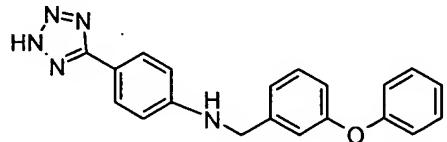


HPLC-MS (Method D): m/z: 296 (M+1); Rt = 3,34 min.

Example 680 (General procedure (H))**[4-(2*H*-Tetrazol-5-yl)phenyl]-[3-(3-trifluoromethylphenoxy)benzyl]amine**

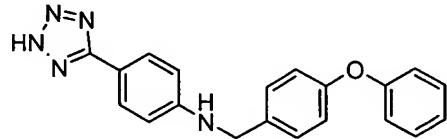
HPLC-MS (Method D): m/z: 412 (M+1); Rt = 5,54 min.

5

Example 681 (General procedure (H))**(3-Phenoxybenzyl)-[4-(2*H*-tetrazol-5-yl)phenyl]amine**

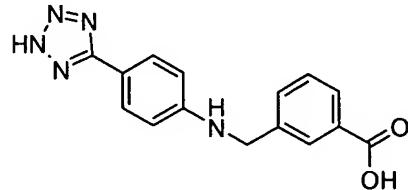
HPLC-MS (Method D): m/z: 344 (M+1); Rt = 5,07 min.

10

Example 682 (General procedure (H))**(4-Phenoxybenzyl)-[4-(2*H*-tetrazol-5-yl)-phenyl]-amine**

HPLC-MS (Method D): m/z: 344 (M+1); Rt = 5,03 min.

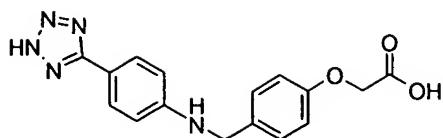
15

Example 683 (General procedure (H))**3-{[4-(2*H*-Tetrazol-5-yl)phenylamino]methyl}benzoic acid**

HPLC-MS (Method D): m/z: 286 (M+1); Rt = 3,47 min.

20

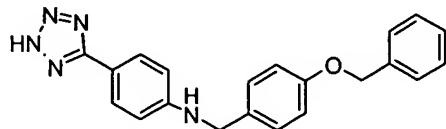
Example 684 (General procedure (H))**(4-{[4-(2*H*-Tetrazol-5-yl)phenylamino]methyl}phenoxy)acetic acid**



HPLC-MS (Method D): m/z: 326 (M+1); Rt = 3,40 min.

Example 685 (General procedure (H))

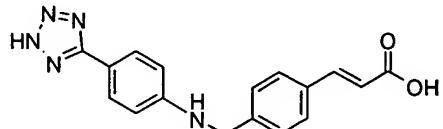
- 5 (4-Benzylaminophenyl)-[4-(2H-tetrazol-5-yl)phenyl]amine



HPLC-MS (Method D): m/z: 358 (M+1); Rt = 5,14 min.

Example 686 (General procedure (H))

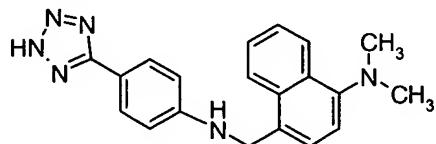
- 10 3-(4-[4-(2H-Tetrazol-5-yl)phenylamino]methyl)phenylacrylic acid



HPLC-MS (Method D): m/z: 322 (M+1); Rt = 3,66 min.

Example 687 (General procedure (H))

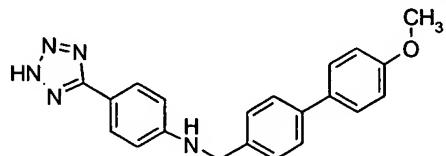
- 15 Dimethyl-(4-[4-(2H-tetrazol-5-yl)phenylamino]methyl)naphthalen-1-yl)amine



HPLC-MS (Method D): m/z: 345 (M+1); Rt = 3,10 min.

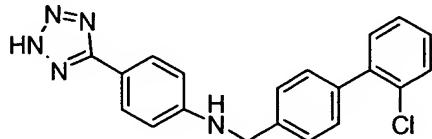
Example 688 (General procedure (H))

- 20 (4'-Methoxybiphenyl-4-ylmethyl)-[4-(2H-tetrazol-5-yl)phenyl]amine

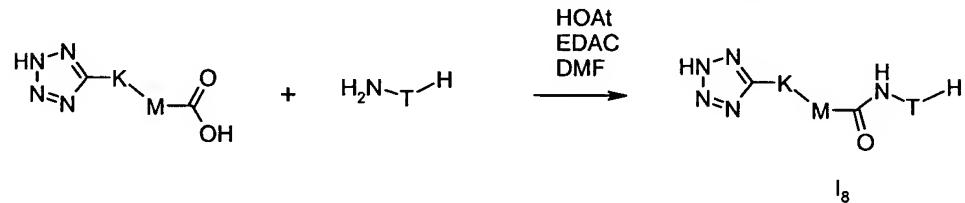


HPLC-MS (Method D): m/z: 358 (M+1); Rt = 5,04 min.

Example 689 (General procedure (H))

(2'-Chlorobiphenyl-4-ylmethyl)-[4-(2*H*-tetrazol-5-yl)-phenyl]-amine

5 HPLC-MS (Method D): m/z: 362 (M+1); Rt = 5,30 min.

General procedure (I) for preparation of compounds of general formula I₈:

wherein K, M and T are as defined above.

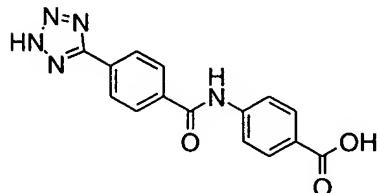
10

This procedure is very similar to general procedure (A), the only difference being the carboxylic acid is containing a tetrazole moiety. When the acylation is complete, the product is isolated by extraction, filtration, chromatography or other methods known to those skilled in the art.

15

The general procedure (I) is further illustrated in the following example 690:

Example 690 (General procedure (I))

4-[4-(2*H*-Tetrazol-5-yl)benzoylamino]benzoic acid

20

To a solution of 4-(2*H*-tetrazol-5-yl)benzoic acid (example 605, 4 mmol) and HOAt (4.2 mmol) in DMF (6 mL) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (4.2 mmol) and the resulting mixture was stirred at room temperature for 1 hour. An aliquot of this HOAt-ester solution (0.45 mL) was mixed with 0.25 mL of a solution of

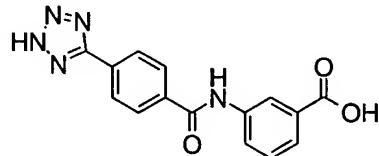
4-aminobenzoic acid (1.2 mmol in 1 mL DMF). (Anilines as hydrochlorides can also be utilised, a slight excess of triethylamine was added to the hydrochloride suspension in DMF prior to mixing with the HOAt-ester.) The resulting mixture was shaken for 3 days at room temperature. 1N hydrochloric acid (2 mL) was added and the mixture was shaken for 16 hours at room temperature. The solid was isolated by centrifugation (alternatively by filtration or extraction) and was washed with water (3 mL). Drying *in vacuo* at 40 °C for 2 days afforded the title compound.

HPLC-MS (Method D): m/z: 310 (M+1); Rt = 2.83 min.

10

Example 691 (General procedure (I))

3-[4-(2H-Tetrazol-5-yl)benzoylamino]benzoic acid

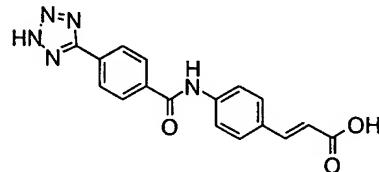


HPLC-MS (Method D): m/z: 310 (M+1); Rt = 2.89 min.

15

Example 692 (General procedure (I))

3-{4-[4-(2H-Tetrazol-5-yl)benzoylamino]phenyl}acrylic acid

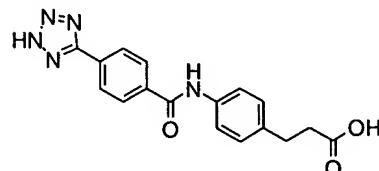


HPLC-MS (Method D): m/z: 336 (M+1); Rt = 3.10 min.

20

Example 693 (General procedure (I))

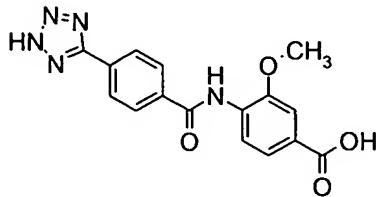
3-{4-[4-(2H-Tetrazol-5-yl)benzoylamino]phenyl}propionic acid



HPLC-MS (Method D): m/z: 338 (M+1); Rt = 2.97 min.

25

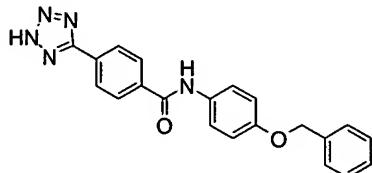
Example 694 (General procedure (I))

N-[3-Methoxy-4-(2*H*-tetrazol-5-yl)benzoyl]amino]benzoic acid

HPLC-MS (Method D): m/z: 340 (M+1); Rt = 3.03 min.

5

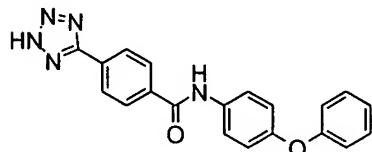
Example 695 (General procedure (I))

N-(4-Benzyloxyphenyl)-4-(2*H*-tetrazol-5-yl)benzamide

HPLC-MS (Method D): m/z: 372 (M+1); Rt = 4.47 min.

10

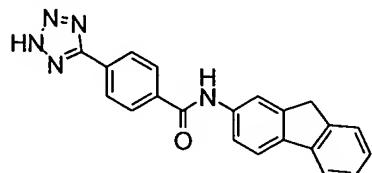
Example 696 (General procedure (I))

N-(4-Phenoxyphenyl)-4-(2*H*-tetrazol-5-yl)benzamide

HPLC-MS (Method D): m/z: 358 (M+1); Rt = 4.50 min.

15

Example 697 (General procedure (I))

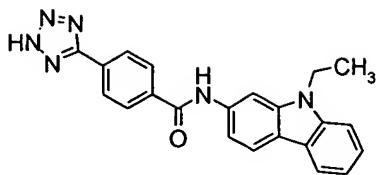
N-(9*H*-Fluoren-2-yl)-4-(2*H*-tetrazol-5-yl)benzamide

HPLC-MS (Method D): m/z: 354 (M+1); Rt = 4.60 min.

20

Example 698 (General procedure (I))

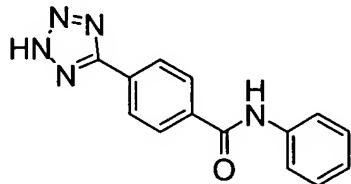
N-(9-Ethyl-9*H*-carbazol-2-yl)-4-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method D): m/z: 383 (M+1); Rt = 4.60 min.

Example 699 (General procedure (I))

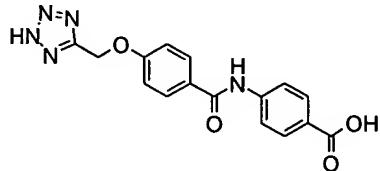
- 5 *N*-Phenyl-4-(2*H*-tetrazol-5-yl)benzamide



HPLC-MS (Method D): m/z: 266 (M+1); Rt = 3.23 min.

Example 700 (General procedure (I))

- 10 4-[4-(2*H*-Tetrazol-5-ylmethoxy)benzoylamino]benzoic acid

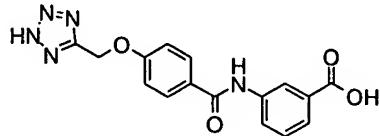


The starting material was prepared as described in example 592.

HPLC-MS (Method D): m/z: 340 (M+1); Rt = 2.83 min.

- 15 Example 701 (General procedure (I))

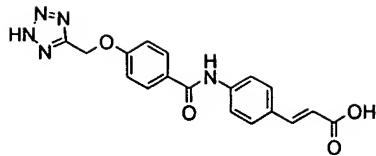
3-[4-(2*H*-Tetrazol-5-ylmethoxy)benzoylamino]benzoic acid



HPLC-MS (Method D): m/z: 340 (M+1); Rt = 2.90 min.

- 20 Example 702 (General procedure (I))

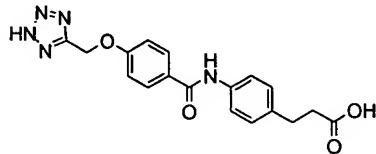
3-{4-[4-(2*H*-Tetrazol-5-ylmethoxy)benzoylamino]phenyl}acrylic acid



HPLC-MS (Method D): m/z: 366 (M+1); Rt = 3.07 min.

Example 703 (General procedure (I))

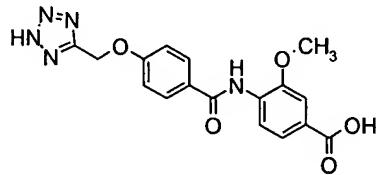
- 5 3-{4-[4-(2H-Tetrazol-5-ylmethoxy)benzoyl]amino}phenylpropionic acid



HPLC-MS (Method D): m/z: 368 (M+1); Rt = 2.97 min.

Example 704 (General procedure (I))

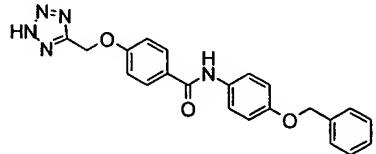
- 10 3-Methoxy-4-[4-(2H-tetrazol-5-ylmethoxy)benzoyl]benzoic acid



HPLC-MS (Method D): m/z: 370 (M+1); Rt = 3.07 min.

Example 705 (General procedure (I))

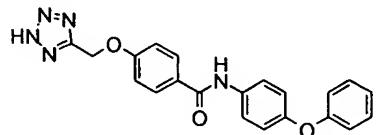
- 15 N-(4-Benzyloxyphenyl)-4-(2H-tetrazol-5-ylmethoxy)benzamide



HPLC-MS (Method D): m/z: 402 (M+1); Rt = 4.43 min.

Example 706 (General procedure (I))

- 20 N-(4-Phenoxyphenyl)-4-(2H-tetrazol-5-ylmethoxy)benzamide

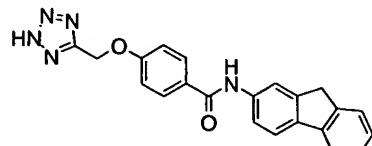


279

HPLC-MS (Method D): m/z: 388 (M+1); Rt = 4.50 min.

Example 707 (General procedure (I))

N-(9H-Fluoren-2-yl)-4-(2*H*-tetrazol-5-ylmethoxy)benzamide

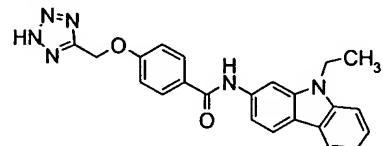


5

HPLC-MS (Method D): m/z: 384 (M+1); Rt = 4.57 min.

Example 708 (General procedure (I))

N-(9-Ethyl-9H-carbazol-2-yl)-4-(2*H*-tetrazol-5-ylmethoxy)benzamide

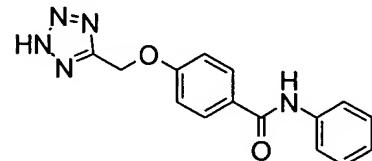


10

HPLC-MS (Method D): m/z: 413 (M+1); Rt = 4.57 min.

Example 709 (General procedure (I))

N-Phenyl-4-(2*H*-tetrazol-5-ylmethoxy)benzamide



15

HPLC-MS (Method D): m/z: 296 (M+1); Rt = 3.23 min.

Example 710 (General procedure (I))

4-[4-(2*H*-Tetrazol-5-ylmethylsulfanyl)benzoylamino]benzoic acid

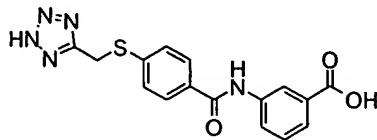


20

The starting material was prepared as described in example 593.

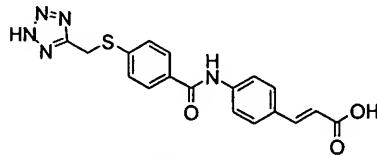
HPLC-MS (Method D): m/z: 356 (M+1); Rt = 2.93 min.

280

Example 711 (General procedure (I))**3-[4-(2*H*-Tetrazol-5-ylmethylsulfanyl)benzoylamino]benzoic acid**

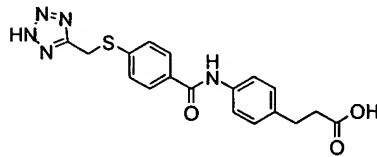
HPLC-MS (Method D): m/z: 356 (M+1); Rt = 3.00 min.

5

Example 712 (General procedure (I))**3-{4-[4-(2*H*-Tetrazol-5-ylmethylsulfanyl)benzoylamino]phenyl}acrylic acid**

HPLC-MS (Method D): m/z: 382 (M+1); Rt = 3.26 min.

10

Example 713 (General procedure (I))**3-{4-[4-(2*H*-Tetrazol-5-ylmethylsulfanyl)benzoylamino]phenyl}propionic acid**

HPLC-MS (Method D): m/z: 384 (M+1); Rt = 3.10 min.

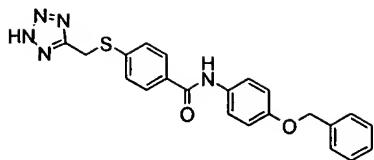
15

Example 714 (General procedure (I))**3-Methoxy-4-[4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzoylamino]benzoic acid**

HPLC-MS (Method D): m/z: 386 (M+1); Rt = 3.20 min.

20

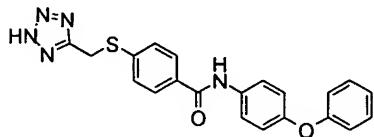
Example 715 (General procedure (I))**N-(4-Benzyloxyphenyl)-4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzamide**



HPLC-MS (Method D): m/z: 418 (M+1); Rt = 4.57 min.

Example 716 (General procedure (I))

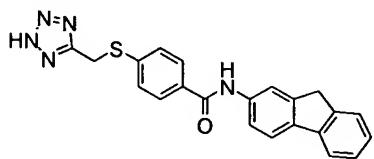
- 5 *N*-(4-Phenoxyphenyl)-4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzamide



HPLC-MS (Method D): m/z: 404 (M+1); Rt = 4.60 min.

Example 717 (General procedure (I))

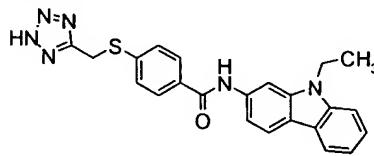
- 10 *N*-(9*H*-Fluoren-2-yl)-4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzamide



HPLC-MS (Method D): m/z: 400 (M+1); Rt = 4.67 min.

Example 718 (General procedure (I))

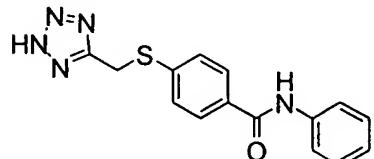
- 15 *N*-(9-Ethyl-9*H*-carbazol-2-yl)-4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzamide



HPLC-MS (Method D): m/z: 429 (M+1); Rt = 4.67 min.

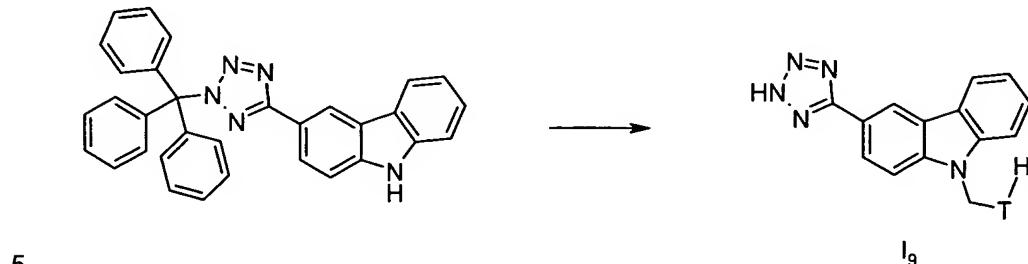
Example 719 (General procedure (I))

- 20 *N*-Phenyl-4-(2*H*-tetrazol-5-ylmethylsulfanyl)benzamide



HPLC-MS (Method D): m/z: 312 (M+1); Rt = 3.40 min.

General procedure (J) for solution phase preparation of amides of general formula I₉:



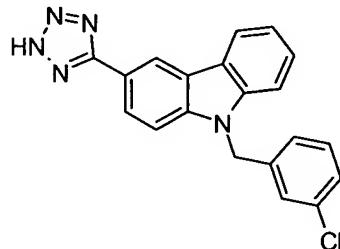
5

wherein T is as defined above.

This general procedure (J) is further illustrated in the following example.

10 Example 720 (General procedure (J)).

9-(3-Chlorobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



3-(2H-Tetrazol-5-yl)-9H-carbazole (example 594, 17 g, 72.26 mmol) was dissolved in N,N-dimethylformamide (150 mL). Triphenylmethyl chloride (21.153 g, 75.88 mmol) and

15 triethylamine (20.14 mL, 14.62 g, 144.50 mmol) were added consecutively. The reaction mixture was stirred for 18 hours at room temperature, poured into water (1.5 L) and stirred for an additional 1 hour. The crude product was filtered off and dissolved in dichloromethane (500 mL). The organic phase was washed with water (2 x 250 mL) and dried with magnesium sulfate (1 h). Filtration followed by concentration yielded a solid which was triturated in heptanes (200 mL). Filtration furnished 3-[2-(triphenylmethyl)-2H-tetrazol-5-yl]-9H-carbazole (31.5 g) which was used without further purification.

¹H-NMR (CDCl₃): δ 8.87 (1H, d), 8.28 (1H, bs), 8.22 (1H, dd), 8.13 (1H, d), 7.49 (1H, d), 7.47-7.19 (18H, m); HPLC-MS (Method C): m/z: 243 (triphenylmethyl); Rt = 5.72 min.

3-[2-(Triphenylmethyl)-2*H*-tetrazol-5-yl]-9*H*-carbazole (200 mg, 0.42 mmol) was dissolved in methyl sulfoxide (1.5 mL). Sodium hydride (34 mg, 60 %, 0.85 mmol) was added, and the resulting suspension was stirred for 30 min at room temperature. 3-Chlorobenzyl chloride (85 μ L, 108 mg, 0.67 mmol) was added, and the stirring was continued at 40 °C for 18 hours.

- 5 The reaction mixture was cooled to ambient temperature and poured into 0.1 N hydrochloric acid (aq.) (15 mL). The precipitated solid was filtered off and washed with water (3 x 10 mL) to furnish 9-(3-chlorobenzyl)-3-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]-9*H*-carbazole, which was dissolved in a mixture of tetrahydrofuran and 6 N hydrochloric acid (aq.) (9:1) (10 mL) and stirred at room temperature for 18 hours. The reaction mixture was poured into water (100 mL). The solid was filtered off and rinsed with water (3 x 10 mL) and dichloromethane (3 x 10 mL) to yield the title compound (127 mg). No further purification was necessary.

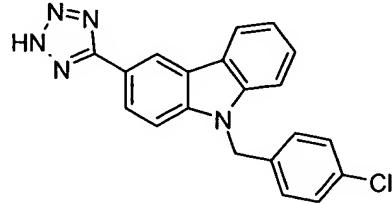
1 H-NMR (DMSO-*d*₆): δ 8.89 (1H, d), 8.29 (1H, d), 8.12 (1H, dd), 7.90 (1H, d), 7.72 (1H, d), 7.53 (1H, t), 7.36-7.27 (4H, m), 7.08 (1H, bt), 5.78 (2H, s); HPLC-MS (Method B): m/z: 360 (M+1); Rt = 5.07 min.

15

The compounds in the following examples were prepared in a similar fashion. Optionally, the compounds can be further purified by recrystallization from e.g. aqueous sodium hydroxide (1 N) or by chromatography.

20 Example 721 (General Procedure (J)).

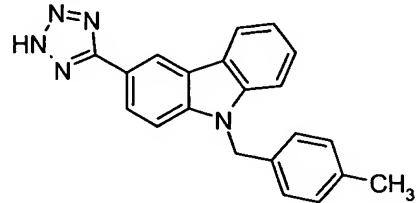
9-(4-Chlorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 360 (M+1); Rt = 4.31 min.

25 Example 722 (General Procedure (J)).

9-(4-Methylbenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

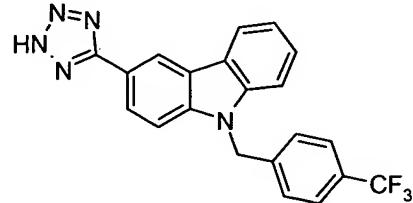


284

HPLC-MS (Method C): m/z: 340 (M+1); Rt = 4.26 min.

Example 723 (General Procedure (J)).

3-(2*H*-Tetrazol-5-yl)-9-(4-trifluoromethylbenzyl)-9*H*-carbazole

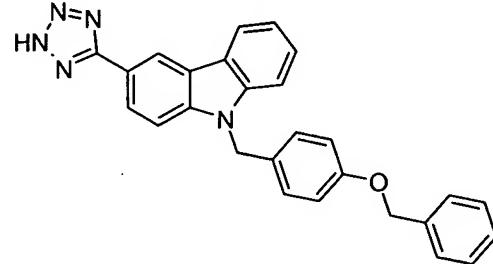


5

HPLC-MS (Method C): m/z: 394 (M+1); Rt = 4.40 min.

Example 724 (General Procedure (J)).

9-(4-Benzyloxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

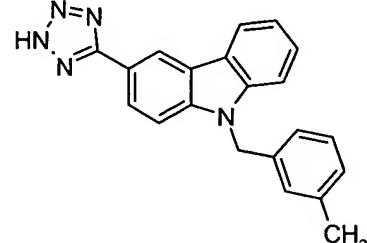


10

HPLC-MS (Method C): m/z: 432 (M+1); Rt = 4.70 min.

Example 725 (General Procedure (J)).

9-(3-Methylbenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

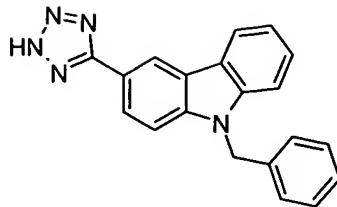


15

HPLC-MS (Method C): m/z: 340 (M+1); Rt = 4.25 min.

Example 726 (General Procedure (J)).

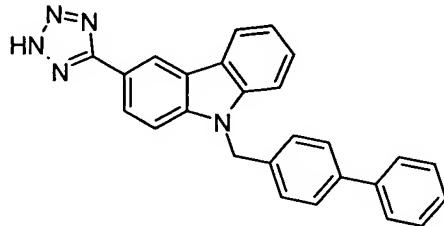
9-Benzyl-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



¹H-NMR (DMSO-d₆): δ 8.91 (1H, dd), 8.30 (1H, d), 8.13 (1H, dd), 7.90 (1H, d), 7.73 (1H, d), 7.53 (1H, t), 7.36-7.20 (6H, m), 5.77 (2H, s).

5 Example 727 (General Procedure (J)).

9-(4-Phenylbenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole

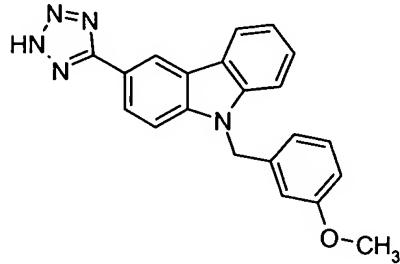


¹H-NMR (DMSO-d₆): δ 8.94 (1H, s), 8.33 (1H, d), 8.17 (1H, dd), 7.95 (1H, d), 7.77 (1H, d), 7.61-7.27 (11H, m), 5.82 (2H, s).

10

Example 728 (General Procedure (J)).

9-(3-Methoxybenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole

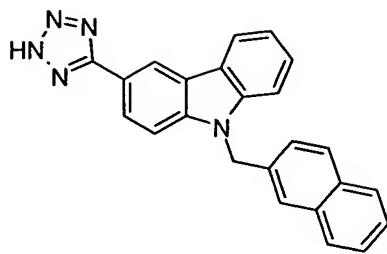


HPLC-MS (Method C): m/z: 356 (M+1); Rt = 3.99 min.

15

Example 729 (General Procedure (J)).

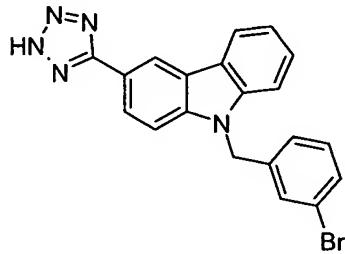
9-(Naphthalen-2-ylmethyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method C): m/z: 376 (M+1); Rt = 4.48 min.

Example 730 (General Procedure (J)).

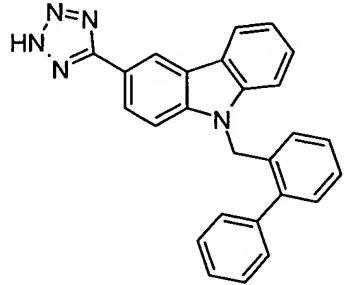
- 5 9-(3-Bromobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method C): m/z: 404 (M+1); Rt = 4.33 min.

Example 731 (General Procedure (J)).

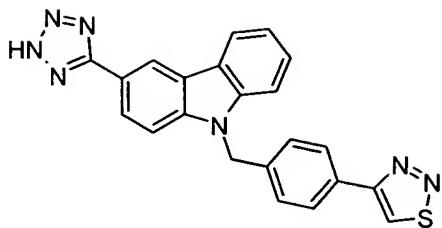
- 10 9-(Biphenyl-2-ylmethyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method C): m/z: 402 (M+1); Rt = 4.80 min.

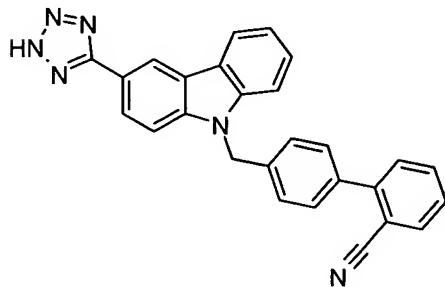
Example 732 (General Procedure (J)).

- 15 3-(2H-Tetrazol-5-yl)-9-[4-(1,2,3-thiadiazol-4-yl)benzyl]-9H-carbazole



Example 733 (General Procedure (J)).

9-(2'-Cyanobiphenyl-4-ylmethyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

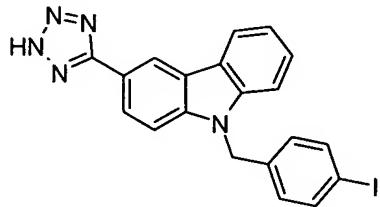


5

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 8.91 (1H, d), 8.31 (1H, d), 8.13 (1H, dd), 7.95 (1H, d), 7.92 (1H, d), 7.78 (1H, d), 7.75 (1H, dt), 7.60-7.47 (5H, m), 7.38-7.28 (3H, m), 5.86 (2H, s); HPLC-MS (Method C): m/z: 427 (M+1); Rt = 4.38 min.

10 **Example 734 (General Procedure (J)).**

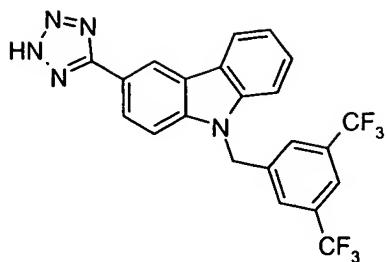
9-(4-Iodobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 452 (M+1); Rt = 4.37 min.

15 **Example 735 (General Procedure (J)).**

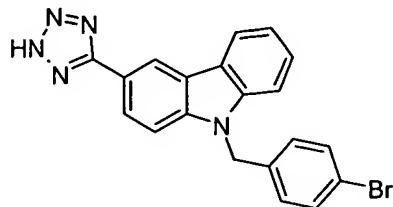
9-(3,5-Bis(trifluoromethyl)benzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 462 (M+1); Rt = 4.70 min.

Example 736 (General Procedure (J)).

5 9-(4-Bromobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

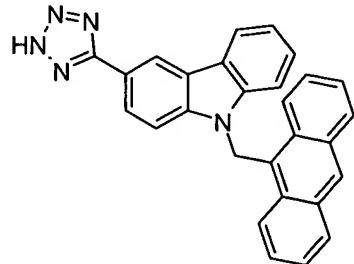


¹H-NMR (DMSO-d₆): δ 8.89 (1H, d), 8.29 (1H, d), 8.11 (1H, dd), 7.88 (1H, d), 7.70 (1H, d), 7.52 (1H, t), 7.49 (2H, d), 7.31 (1H, t), 7.14 (2H, d), 5.74 (2H, s); HPLC-MS (Method C): m/z: 404 (M+1); Rt = 4.40 min.

10

Example 737 (General Procedure (J)).

9-(Anthracen-9-ylmethyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

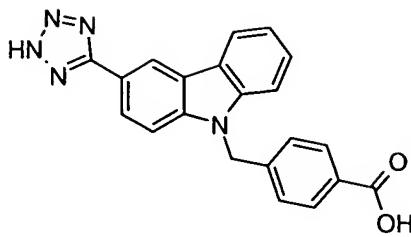


HPLC-MS (Method C): m/z: 426 (M+1); Rt = 4.78 min.

15

Example 738 (General Procedure (J)).

9-(4-Carboxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

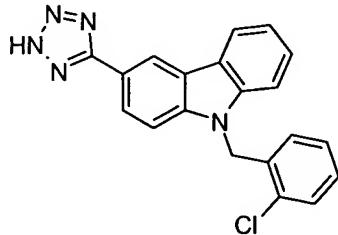


3.6 fold excess sodium hydride was used.

- 5 $^1\text{H-NMR}$ (DMSO- d_6): δ 12.89 (1H, bs), 8.89 (1H, d), 8.30 (1H, d), 8.10 (1H, dd), 7.87 (1H, d), 7.86 (2H, d), 7.68 (1H, d), 7.51 (1H, t), 7.32 (1H, t), 7.27 (2H, d), 5.84 (2H, s); HPLC-MS (Method C): m/z: 370 (M+1); Rt = 3.37 min.

Example 739 (General Procedure (J)).

9-(2-Chlorobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole

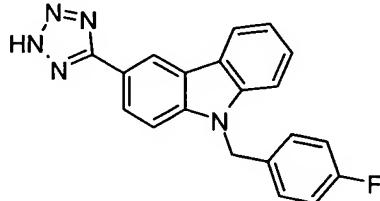


10

HPLC-MS (Method B): m/z: 360 (M+1); Rt = 5.30 min.

Example 740 (General Procedure (J)).

9-(4-Fluorobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



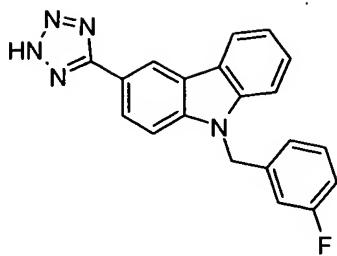
15

$^1\text{H-NMR}$ (DMSO- d_6): δ 8.88 (1H, d), 8.28 (1H, d), 8.10 (1H, dd), 7.89 (1H, d), 7.72 (1H, d), 7.52 (1H, t), 7.31 (1H, t), 7.31-7.08 (4H, m), 5.74 (2H, s); HPLC-MS (Method C): m/z: 344 (M+1); Rt = 4.10 min.

20 Example 741 (General Procedure (J)).

9-(3-Fluorobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole

290

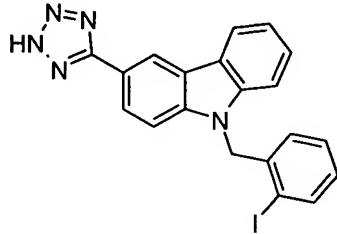


¹H-NMR (DMSO-d₆): δ 8.89 (1H, d), 8.29 (1H, d), 8.12 (1H, dd), 7.90 (1H, d), 7.72 (1H, d), 7.53 (1H, t), 7.37-7.27 (2H, m), 7.12-7.02 (2H, m), 6.97 (1H, d), 5.78 (2H, s); HPLC-MS (Method C): m/z: 344 (M+1); Rt = 4.10 min.

5

Example 742 (General Procedure (J)).

9-(2-Iodobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole

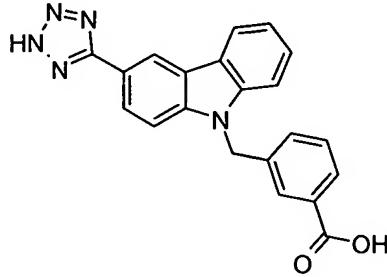


HPLC-MS (Method C): m/z: 452 (M+1); Rt = 4.58 min.

10

Example 743 (General Procedure (J)).

9-(3-Carboxybenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole

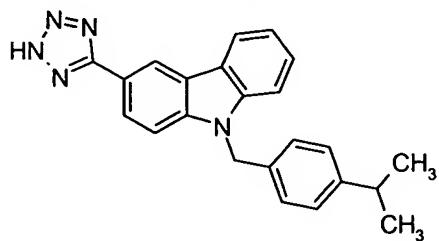


3.6 fold excess sodium hydride was used.

15

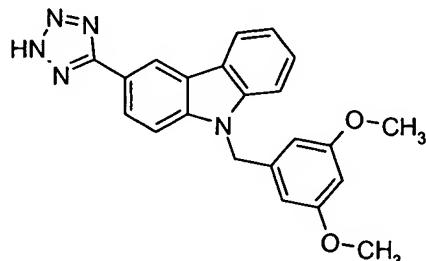
¹H-NMR (DMSO-d₆): δ 12.97 (1H, bs), 8.90 (1H, bs), 8.30 (1H, d), 8.12 (1H, bd), 7.89 (1H, d), 7.82 (1H, m), 7.77 (1H, bs), 7.71 (1H, d), 7.53 (1H, t), 7.46-7.41 (2H, m), 7.32 (1H, t), 5.84 (2H, s); HPLC-MS (Method C): m/z: 370 (M+1); Rt = 3.35 min.

Example 744 (General Procedure (J)).

9-[4-(2-Propyl)benzyl]-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

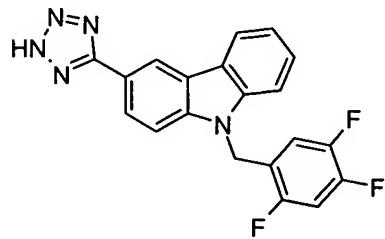
¹H-NMR (DMSO-*d*₆): δ 8.87 (1H, d), 8.27 (1H, d), 8.10 (1H, dd), 7.87 (1H, d), 7.71 (1H, d),
 5 7.51 (1H, t), 7.31 (1H, t), 7.15 (2H, d), 7.12 (2H, d), 5.69 (2H, s), 2.80 (1H, sept), 1.12 (6H,
 d); HPLC-MS (Method C): m/z: 368 (M+1); Rt = 4.73 min.

Example 745 (General Procedure (J)).

9-(3,5-Dimethoxybenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

¹⁰ HPLC-MS (Method C): m/z: 386 (M+1); Rt = 4.03 min.

Example 746 (General Procedure (J)).

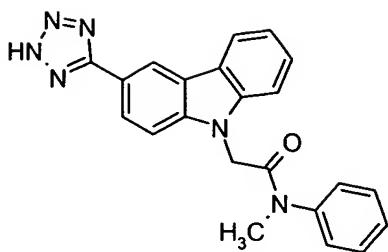
3-(2*H*-Tetrazol-5-yl)-9-(2,4,5-trifluorobenzyl)-9*H*-carbazole

¹⁵ HPLC-MS (Method B): m/z: 380 (M+1); Rt = 5.00 min.

Example 747 (General Procedure (J)).

N-Methyl-*N*-phenyl-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide

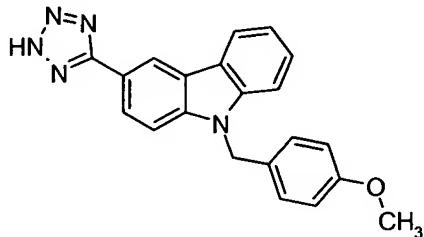
292



HPLC-MS (Method B): m/z: 383 (M+1); Rt = 4.30 min.

Example 748 (General Procedure (J)).

5 9-(4-Methoxybenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole

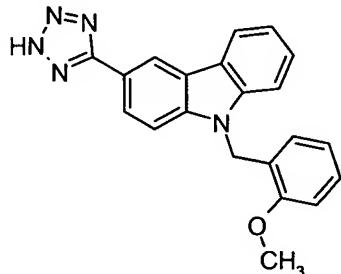


¹H-NMR (DMSO-d₆): δ 8.86 (1H, d), 8.26 (1H, d), 8.10 (1H, dd), 7.90 (1H, d), 7.73 (1H, d), 7.51 (1H, t), 7.30 (1H, t), 7.18 (2H, d), 6.84 (2H, d), 5.66 (2H, s), 3.67 (3H, s); HPLC-MS (Method B): m/z: 356 (M+1); Rt = 4.73 min.

10

Example 749 (General Procedure (J)).

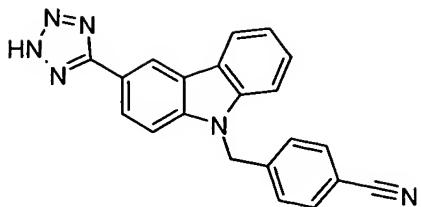
9-(2-Methoxybenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



¹H-NMR (DMSO-d₆): δ 8.87 (1H, d), 8.27 (1H, d), 8.09 (1H, dd), 7.77 (1H, d), 7.60 (1H, d), 7.49 (1H, t), 7.29 (1H, t), 7.23 (1H, bt), 7.07 (1H, bd), 6.74 (1H, bt), 6.61 (1H, bd), 5.65 (2H, s), 3.88 (3H, s); HPLC-MS (Method B): m/z: 356 (M+1); Rt = 4.97 min.

Example 750 (General Procedure (J)).

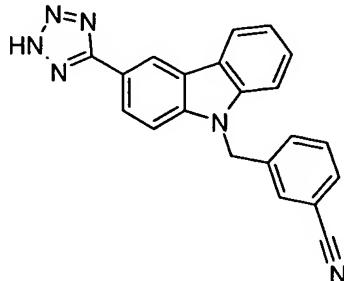
9-(4-Cyanobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method C): m/z: 351 (M+1); Rt = 3.74 min.

Example 751 (General Procedure (J)).

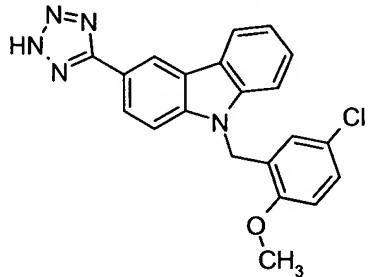
- 5 9-(3-Cyanobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method C): m/z: 351 (M+1); Rt = 3.73 min.

Example 752 (General Procedure (J)).

- 10 9-(5-Chloro-2-methoxybenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole

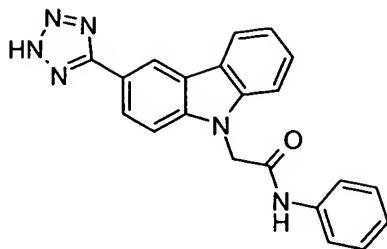


¹H-NMR (DMSO-d₆): δ 8.87 (1H, d), 8.35 (1H, d), 8.10 (1H, dd), 7.73 (1H, d), 7.59 (1H, d), 7.49 (1H, t), 7.29 (1H, t), 7.27 (1H, dd), 7.11 (1H, d), 6.51 (1H, d), 5.63 (2H, s), 3.88 (3H, s); HPLC-MS (Method C): m/z: 390 (M+1); Rt = 4.37 min.

- 15

Example 753 (General Procedure (J)).

N-Phenyl-2-[3-(2H-tetrazol-5-yl)carbazol-9-yl]acetamide

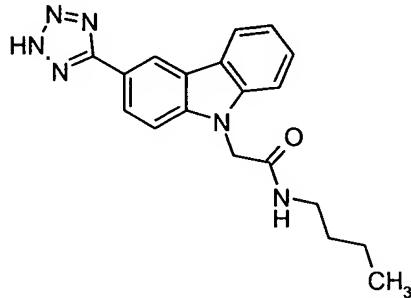


¹H-NMR (DMSO-d₆): δ 10.54 (1H, s), 8.87 (1H, bs), 8.27 (1H, d), 8.12 (1H, bd), 7.83 (1H, d), 7.66 (1H, d), 7.61 (2H, d), 7.53 (1H, t), 7.32 (1H, t), 7.32 (2H, t), 7.07 (1H, t), 5.36 (2H, s); HPLC-MS (Method C): m/z: 369 (M+1); Rt = 3.44 min.

5

Example 754 (General Procedure (J)).

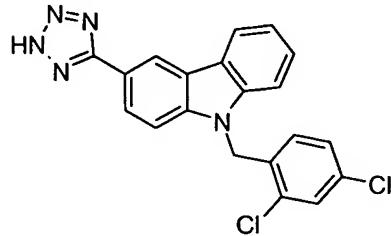
N-Butyl-2-[3-(2H-tetrazol-5-yl)carbazol-9-yl]acetamide



¹H-NMR (DMSO-d₆): δ 8.85 (1H, d), 8.31 (1H, t), 8.25 (1H, d), 8.10 (1H, dd), 7.75 (1H, d), 10 7.58 (1H, d), 7.52 (1H, t), 7.30 (1H, t), 5.09 (2H, s), 3.11 (2H, q), 1.42 (2H, quint), 1.30 (2H, sext), 0.87 (3H, t); HPLC-MS (Method C): m/z: 349 (M+1); Rt = 3.20 min.

Example 755 (General Procedure (J)).

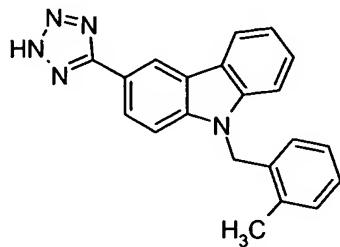
9-(2,4-Dichlorobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



15

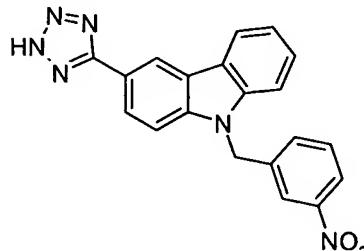
¹H-NMR (DMSO-d₆): δ 8.92 (1H, d), 8.32 (1H, d), 8.09 (1H, dd), 7.76 (1H, d), 7.74 (1H, d), 7.58 (1H, d), 7.51 (1H, t), 7.33 (1H, t), 7.23 (1H, dd), 6.42 (1H, d), 5.80 (2H, s); HPLC-MS (Method B): m/z: 394 (M+1); Rt = 5.87 min.

Example 756 (General Procedure (J)).

9-(2-Methylbenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

¹H-NMR (DMSO-*d*₆): δ 8.92 (1H, d), 8.32 (1H, d), 8.08 (1H, dd), 7.72 (1H, d), 7.55 (1H, d),
 5 7.48 (1H, t), 7.32 (1H, t), 7.26 (1H, d), 7.12 (1H, t), 6.92 (1H, t), 6.17 (1H, d), 5.73 (2H, s),
 2.46 (3H, s); HPLC-MS (Method B): m/z: 340 (M+1); Rt = 5.30 min.

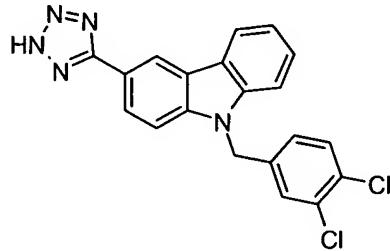
Example 757 (General Procedure (J)).

9-(3-Nitrobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

10

HPLC-MS (Method C): m/z: 371 (M+1); Rt = 3.78 min.

Example 758 (General Procedure (J)).

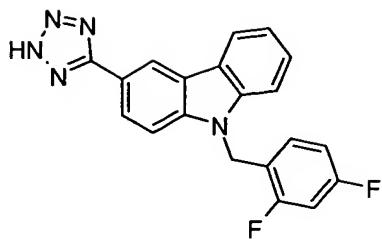
9-(3,4-Dichlorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

15

HPLC-MS (Method B): m/z: 394 (M+1); Rt = 5.62 min.

Example 759 (General Procedure (J)).

9-(2,4-Difluorobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole

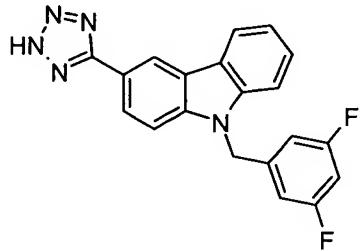


¹H-NMR (DMSO-*d*₆): δ 8.89 (1H, d), 8.29 (1H, d), 8.11 (1H, dd), 7.88 (1H, d), 7.69 (1H, d), 7.52 (1H, t), 7.36-7.24 (2H, m), 7.06-6.91 (2H, m), 5.78 (2H, s); HPLC-MS (Method B): m/z: 362 (M+1); Rt = 5.17 min.

5

Example 760 (General Procedure (J)).

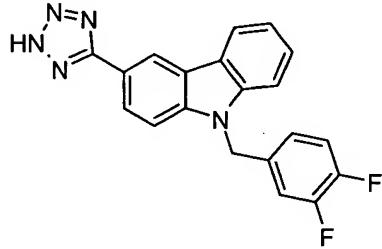
9-(3,5-Difluorobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



¹H-NMR (DMSO-*d*₆): δ 8.90 (1H, bs), 8.31 (1H, d), 8.13 (1H, bd), 7.90 (1H, d), 7.73 (1H, d), 7.54 (1H, t), 7.34 (1H, t), 7.14 (1H, t), 6.87 (2H, bd), 5.80 (2H, s); HPLC-MS (Method B): m/z: 362 (M+1); Rt = 5.17 min.

Example 761 (General Procedure (J)).

9-(3,4-Difluorobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole

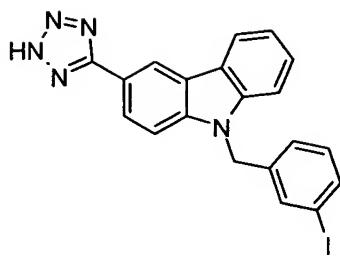


15

¹H-NMR (DMSO-*d*₆): δ 8.89 (1H, bs), 8.29 (1H, d), 8.12 (1H, bd), 7.92 (1H, d), 7.74 (1H, d), 7.54 (1H, t), 7.42-7.25 (3H, m), 6.97 (1H, bm), 5.75 (2H, s); HPLC-MS (Method B): m/z: 362 (M+1); Rt = 5.17 min.

20 Example 762 (General Procedure (J)).

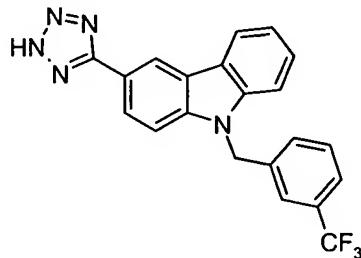
9-(3-Iodobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method B): m/z: 452 (M+1); Rt = 5.50 min.

Example 763 (General Procedure (J)).

- 5 3-(2H-Tetrazol-5-yl)-9-[3-(trifluoromethyl)benzyl]-9H-carbazole

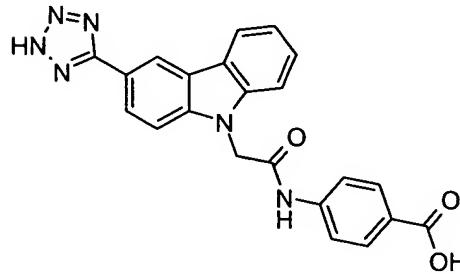


¹H-NMR (DMSO-d₆): δ 8.89 (1H, d), 8.30 (1H, d), 8.11 (1H, dd), 7.90 (1H, d), 7.72 (1H, d), 7.67 (1H, bs), 7.62 (1H, bd), 7.53 (1H, t), 7.50 (1H, bt), 7.33 (1H, bd), 7.32 (1H, t), 5.87 (2H, s); HPLC-MS (Method B): m/z: 394 (M+1); Rt = 5.40 min.

10

Example 764 (General Procedure (J)).

N-(4-Carboxyphenyl)-2-[3-(2H-tetrazol-5-yl)carbazol-9-yl]acetamide



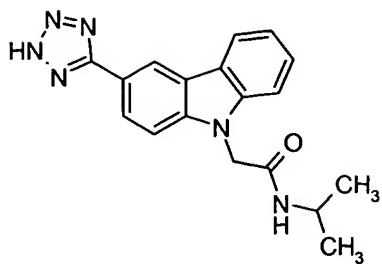
15 3.6 fold excess sodium hydride was used.

HPLC-MS (Method B): m/z: 413 (M+1); Rt = 3.92 min.

Example 765 (General Procedure (J)).

20 N-(2-Propyl)-2-[3-(2H-tetrazol-5-yl)carbazol-9-yl]acetamide

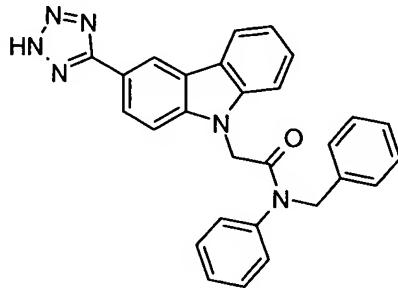
298



HPLC-MS (Method B): m/z: 335 (M+1); Rt = 3.70 min.

Example 766 (General Procedure (J)).

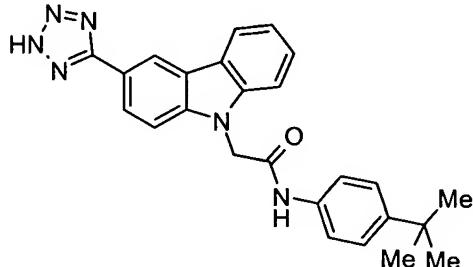
- 5 *N*-Benzyl-*N*-phenyl-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide



HPLC-MS (Method B): m/z: 459 (M+1); Rt = 5.37 min.

Example 767 (General Procedure (J)).

- 10 *N*-[4-(2-Methyl-2-propyl)phenyl]-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide

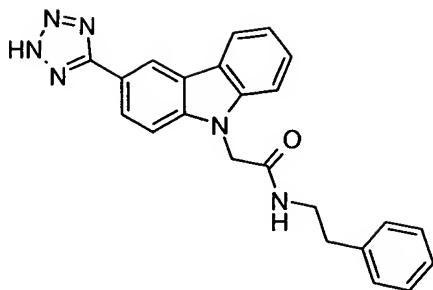


HPLC-MS (Method B): m/z: 425 (M+1); Rt = 5.35 min.

Example 768 (General Procedure (J)).

- 15 *N*-Phenethyl-2-[3-(2*H*-tetrazol-5-yl)carbazol-9-yl]acetamide

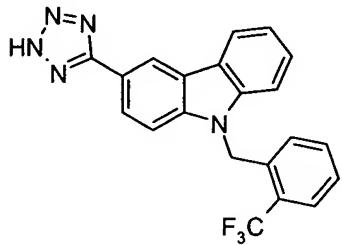
299



HPLC-MS (Method C): m/z: 397 (M+1); Rt = 3.43 min.

Example 769 (General Procedure (J)).

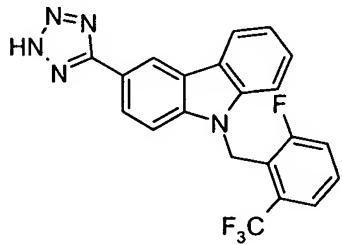
- 5 3-(2H-Tetrazol-5-yl)-9-[2-(trifluoromethyl)benzyl]-9H-carbazole



HPLC-MS (Method C): m/z: 394 (M+1); Rt = 4.44 min.

Example 770 (General Procedure (J)).

- 10 9-[2-Fluoro-6-(trifluoromethyl)benzyl]-3-(2H-tetrazol-5-yl)-9H-carbazole

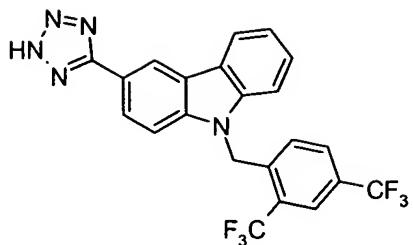


HPLC-MS (Method C): m/z: 412 (M+1); Rt = 4.21 min.

Example 771 (General Procedure (J)).

- 15 9-[2,4-Bis(trifluoromethyl)benzyl]-3-(2H-tetrazol-5-yl)-9H-carbazole

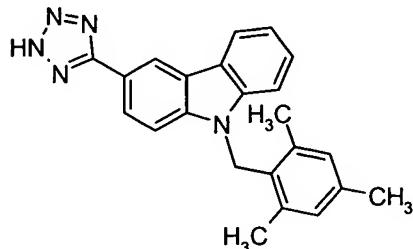
300



HPLC-MS (Method C): m/z: 462 (M+1); Rt = 4.82 min.

Example 772 (General Procedure (J)).

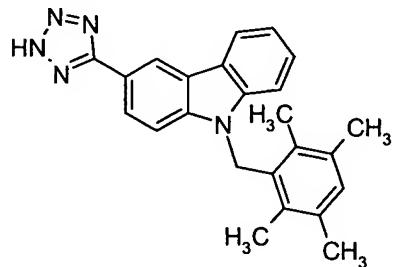
- 5 3-(2*H*-Tetrazol-5-yl)-9-(2,4,6-trimethylbenzyl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 368 (M+1); Rt = 4.59 min.

Example 773 (General Procedure (J)).

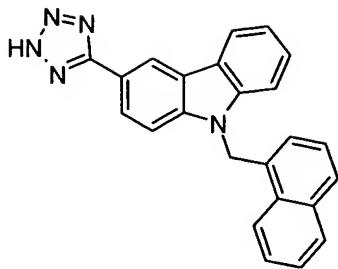
- 10 9-(2,3,5,6-Tetramethylbenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 382 (M+1); Rt = 4.47 min.

Example 774 (General Procedure (J)).

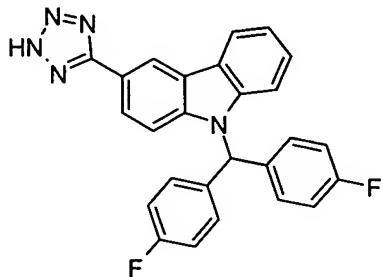
- 15 9-[(Naphthalen-1-yl)methyl]-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole



HPLC-MS (Method C): m/z: 376 (M+1); Rt = 4.43 min.

Example 775 (General Procedure (J)).

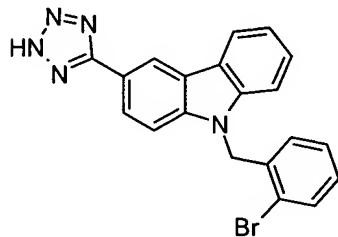
- 5 9-[Bis(4-fluorophenyl)methyl]-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method C): m/z: 438 (M+1); Rt = 4.60 min.

Example 776 (General Procedure (J)).

- 10 9-(2-Bromobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole

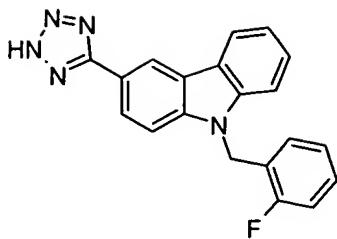


HPLC-MS (Method C): m/z: 404 (M+1); Rt = 4.50 min.

Example 777 (General Procedure (J)).

- 15 9-(2-Fluorobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole

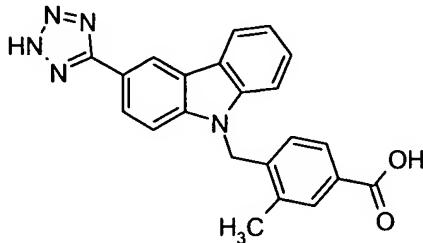
302



HPLC-MS (Method C): m/z: 344 (M+1); Rt = 4.09 min.

Example 778 (General Procedure (J)).

- 5 9-(4-Carboxy-2-methylbenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole

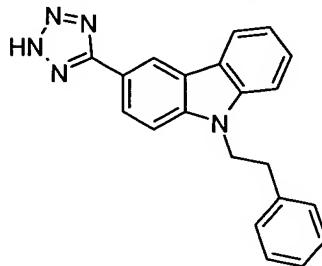


In this preparation, a 3.6-fold excess of sodium hydride was used.

HPLC-MS (Method C): m/z: 384 (M+1); Rt = 3.56 min.

- 10 Example 779 (General Procedure (J)).

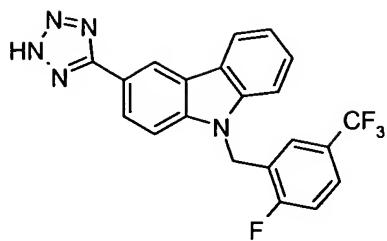
9-(2-Phenylethyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method C): m/z: 340 (M+1); Rt = 4.08 min.

- 15 Example 780 (General Procedure (J)).

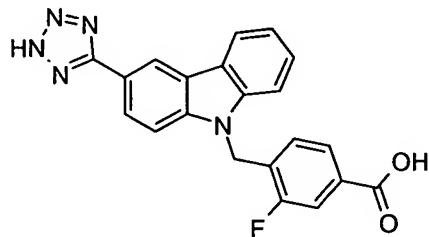
9-[2-Fluoro-5-(trifluoromethyl)benzyl]-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method C): m/z: 412 (M+1); Rt = 4.34 min.

Example 781 (General Procedure (J)).

5 9-(4-Carboxy-2-fluorobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



3-Fluoro-4-methylbenzoic acid (3.0 g, 19.5 mmol) and benzoyl peroxide (0.18 g, 0.74 mmol) were suspended in benzene. The mixture was purged with N₂ and heated to reflux. N-Bromosuccinimide (3.47 g, 19.5 mmol) was added portionwise, and reflux was maintained for

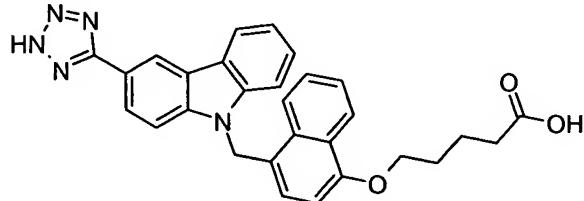
10 18 hours. The reaction mixture was concentrated, and the residue was washed with water (20 mL) at 70 °C for 1 hour. The crude product was isolated by filtration and washed with additional water (2 x 10 mL). The dry product was recrystallized from heptanes. Filtration furnished 4-bromomethyl-3-fluorobenzoic acid (1.92 g) which was used in the following step according to General Procedure (J).

15 In this preparation, a 3.6-fold excess of sodium hydride was used.

HPLC-MS (Method C): m/z: 388 (M+1); Rt = 3.49 min.

Example 782 (General Procedure (J)).

5-{4-[(3-(2H-Tetrazol-5-yl)carbazol-9-yl)methyl]naphthalen-1-yl}oxy}pentanoic Acid



20

5-[(4-Formynaphthalen-1-yl)oxy]pentanoic acid intermediate obtained in example 470(3.0 g, 11.0 mmol) was dissolved in a mixture of methanol and tetrahydrofuran (9:1) (100 mL), and

sodium borohydride (1.67 g, 44.1 mmol) was added portionwise at ambient temperature. After 30 minutes, the reaction mixture was concentrated to 50 mL and added to hydrochloric acid (0.1 N, 500 mL). Additional hydrochloric acid (1 N, 40 mL) was added, and 5-[(4-hydroxymethyl-naphthalen-1-yl)oxy]pentanoic acid (2.90 g) was collected by filtration. To the 5 crude product was added concentrated hydrochloric acid (100 mL), and the suspension was stirred vigorously for 48 hours at room temperature. The crude product was filtered off and washed with water, until the pH was essentially neutral. The material was washed with heptanes to furnish 5-[(4-chloromethyl)naphthalen-1-yl)oxy]pentanoic acid (3.0 g) which was used in the following step according to General Procedure (J).

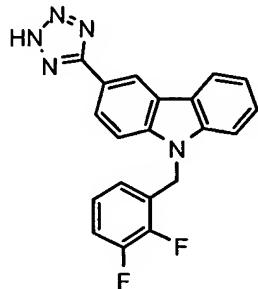
10

In this preparation, a 3.6-fold excess of sodium hydride was used.

HPLC-MS (Method C): m/z: 492 (M+1); Rt = 4.27 min.

Example 783 (General procedure (J))

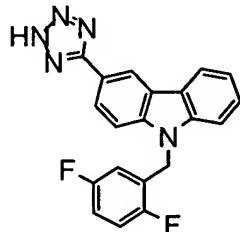
15 9-(2,3-Difluorobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method C): m/z= 362 (M+1); Rt = 4.13 min.

Example 784 (General procedure (J))

20 9-(2,5-Difluorobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method C): m/z = 362 (M+1); Rt = 4.08 min.

Example 785 (General procedure (J))

9-Pentafluorophenylmethyl-3-(2H-tetrazol-5-yl)-9H-carbazole

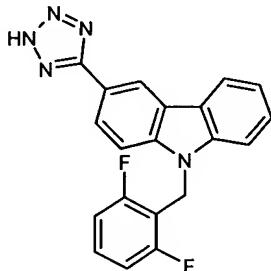


HPLC-MS (Method C): m/z = 416 (M+1); Rt = 4.32 min.

5

Example 786 (General procedure (J))

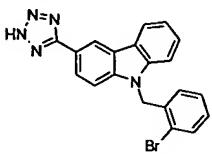
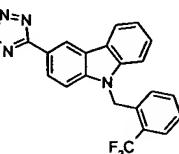
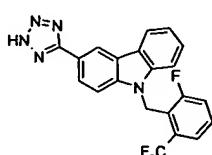
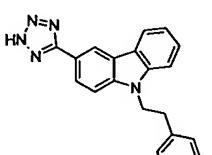
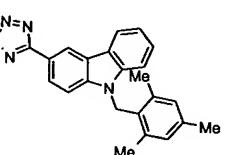
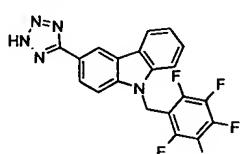
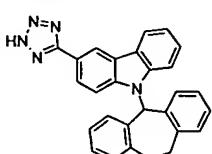
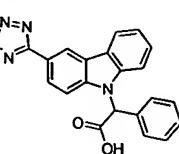
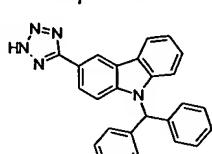
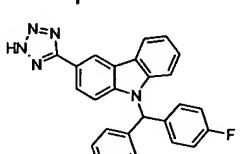
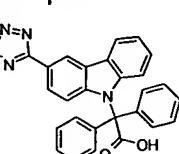
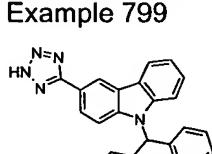
9-(2,6-Difluorobenzyl)-3-(2H-tetrazol-5-yl)-9H-carbazole



HPLC-MS (Method C): m/z = 362 (M+1); Rt = 3.77 min.

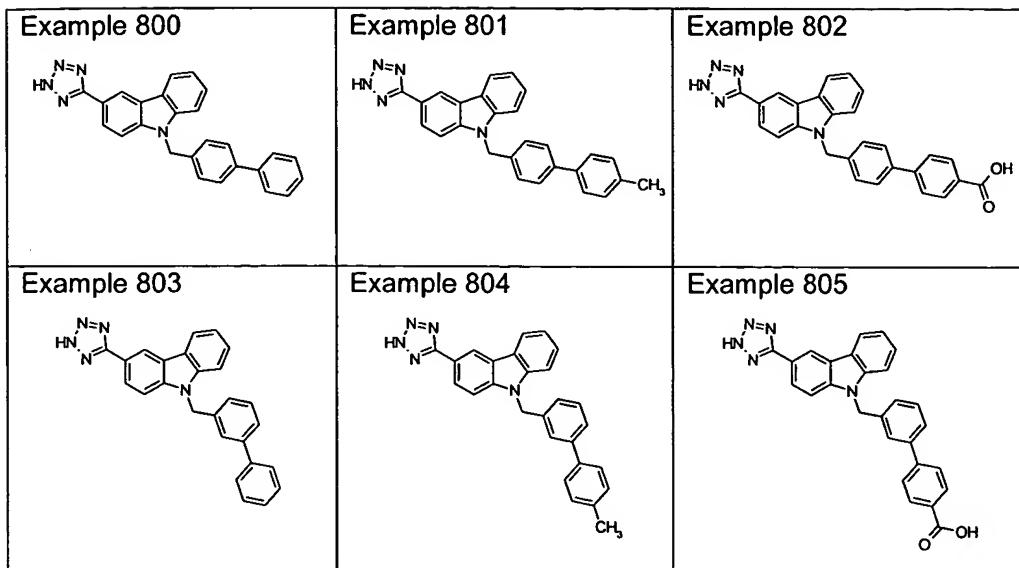
10

Further compounds of the invention that may be prepared according to general procedure (J), and includes:

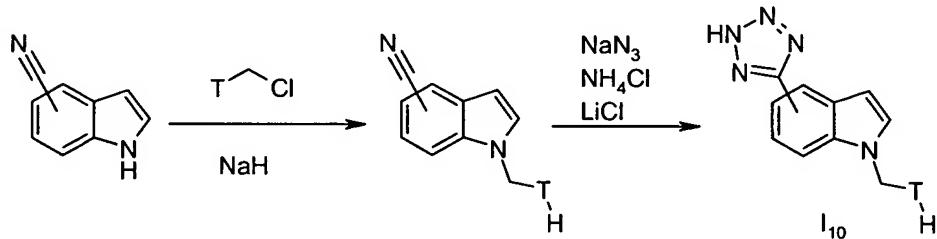
Example 787 	Example 788 	Example 789 
Example 790 	Example 791 	Example 792 
Example 793 	Example 794 	Example 795 
Example 796 	Example 797 	Example 798 
Example 799 		

The following compounds of the invention may be prepared eg. from 9-(4-bromobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole (example 736) or from 9-(3-bromobenzyl)-3-(2*H*-tetrazol-5-yl)-9*H*-carbazole (example 730) and aryl boronic acids *via* the Suzuki coupling reaction eg as

- 5 described in Littke, Dai & Fu *J. Am. Chem. Soc.*, **2000**, *122*, 4020-8 (or references cited therein), or using the methodology described in general procedure (E), optionally changing the palladium catalyst to bis(*tri-tert*-butylphosphine)palladium (0).



General procedure (K) for preparation of compounds of general formula I₁₀:



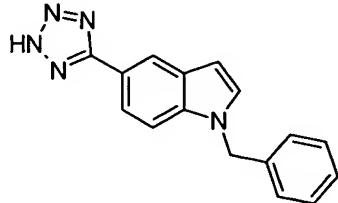
5

wherein T is as defined above.

The general procedure (K) is further illustrated by the following example:

Example 806 (General procedure (K)).

10 1-Benzyl-5-(2H-tetrazol-5-yl)-1H-indole



5-Cyanoindole (1.0 g, 7.0 mmol) was dissolved in N,N-dimethylformamide (14 mL) and cooled in an ice-water bath. Sodium hydride (0.31 g, 60 %, 7.8 mmol) was added, and the resulting suspension was stirred for 30 min. Benzyl chloride (0.85 mL, 0.94 g, 7.4 mmol) was

added, and the cooling was discontinued. The stirring was continued for 65 hours at room temperature. Water (150 mL) was added, and the mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic phases were washed with brine (30 mL) and dried with sodium sulfate (1 hour). Filtration and concentration yielded the crude material. Purification by flash chromatography on silica gel eluting with ethyl acetate/heptanes = 1:3 afforded 1.60 g 1-benzyl-1*H*-indole-5-carbonitrile.

HPLC-MS (Method C): m/z: 233 (M+1); Rt = 4.17 min.

10 1-Benzyl-1*H*-indole-5-carbonitrile was transformed into 1-benzyl-5-(2*H*-tetrazol-5-yl)-1*H*-indole by the method described in general procedure (J) and in example 594. Purification was done by flash chromatography on silica gel eluting with dichloromethane/methanol = 9:1.

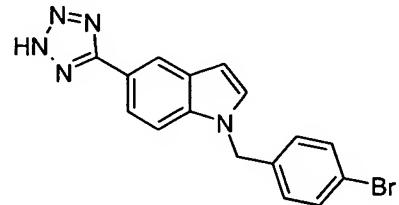
HPLC-MS (Method C): m/z: 276 (M+1); Rt = 3.35 min.

15

The compounds in the following examples were prepared by the same procedure.

Example 807 (General procedure (K)).

1-(4-Bromobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole

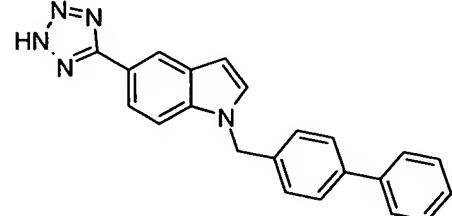


20

HPLC-MS (Method C): m/z: 354 (M+1); Rt = 3.80 min.

Example 808 (General procedure (K)).

1-(4-Phenylbenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



25

¹H-NMR (200 MHz, DMSO-d₆): δ = 5.52 (2H, s), 6.70 (1H, d), 7.3-7.45 (6H, m), 7.6 (4H, m), 7.7-7.8 (2H, m), 7.85(1H, dd), 8.35 (1H, d).

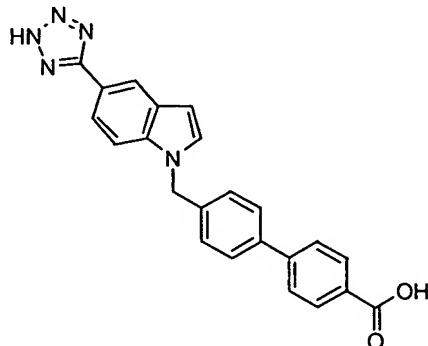
Calculated for C₂₂H₁₇N₅, H₂O:

73.32% C; 5.03% H; 19.43% N. Found:

73.81% C; 4.90% H; 19.31% N.

5 Example 809

4'-(5-(2H-Tetrazol-5-yl)indol-1-ylmethyl)biphenyl-4-carboxylic acid



5-(2H-Tetrazol-5-yl)-1H-indole (Syncom BV, Groningen, NL) (1.66g, 8.9 mmol) was treated with trityl chloride (2.5 g, 8.9 mmol) and triethyl amine (2.5 mL, 17.9 mmol) in DMF(25 mL) by stirring at RT overnight. The resulting mixture was treated with water. The gel was isolated, dissolved in methanol, treated with activated carbon; filtered and evaporated to dryness *in vacuo*. This afforded 3.6 g (94%) of crude 5-(2-trityl-2H-tetrazol-5-yl)-1H-indole.

HPLC-MS (Method C): m/z = 450 (M+23); Rt. = 5.32 min.

15

4-Methylphenylbenzoic acid (5 g, 23.5 mmol) was mixed with CCl₄ (100 mL) and under an atmosphere of nitrogen, the slurry was added *N*-Bromosuccinimide (4.19 g, 23.55 mmol) and dibenzoyl peroxide (0.228 g, 0.94 mmol). The mixture was subsequently heated to reflux for 0.5 hour. After cooling, DCM and water (each 30 mL) were added. The resulting precipitate was isolated, washed with water and a small amount of methanol. The solid was dried *in vacuo* to afford 5.27 g (77%) of 4'-bromomethylbiphenyl-4-carboxylic acid.

HPLC-MS (Method C): m/z = 291 (M+1); Rt. = 3.96 min.

25 5-(2-Trityl-2H-tetrazol-5-yl)-1H-indole (3.6 g, 8.4 mmol) was dissolved in DMF (100 mL). Under nitrogen, NaH (60 % suspension in mineral oil, 34 mmol) was added slowly. 4'-Bromomethylbiphenyl-4-carboxylic acid (2.7 g, 9.2 mmol) was added over 5 minutes and the

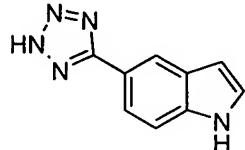
resulting slurry was heated at 40 °C for 16 hours. The mixture was poured into water (100mL) and the precipitate was isolated by filtration and treated with THF/6N HCl (9/1) (70 mL) at room temperature for 16 hours. The mixture was subsequently evaporated to dryness *in vacuo*, the residue was treated with water and the solid was isolated by filtration and 5 washed thoroughly 3 times with DCM. The solid was dissolved in hot THF (400 mL) treated with activated carbon and filtered. The filtrate was evaporated *in vacuo* to dryness. This afforded 1.6 g (50%) of the title compound.

HPLC-MS (Method C): m/z = 396 (M+1); Rt. = 3.51 min.

10

Example 810 (General procedure (K)).

5-(2*H*-Tetrazol-5-yl)-1*H*-indole



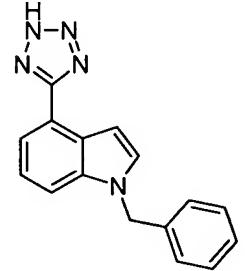
5-(2*H*-Tetrazol-5-yl)-1*H*-indole was prepared from 5-cyanoindole according to the method

15 described in example 594.

HPLC-MS (Method C): m/z: 186 (M+1); Rt = 1.68 min.

Example 811 (General procedure (K)).

20 1-Benzyl-4-(2*H*-tetrazol-5-yl)-1*H*-indole



1-Benzyl-1*H*-indole-4-carbonitrile was prepared from 4-cyanoindole according to the method described in example 806.

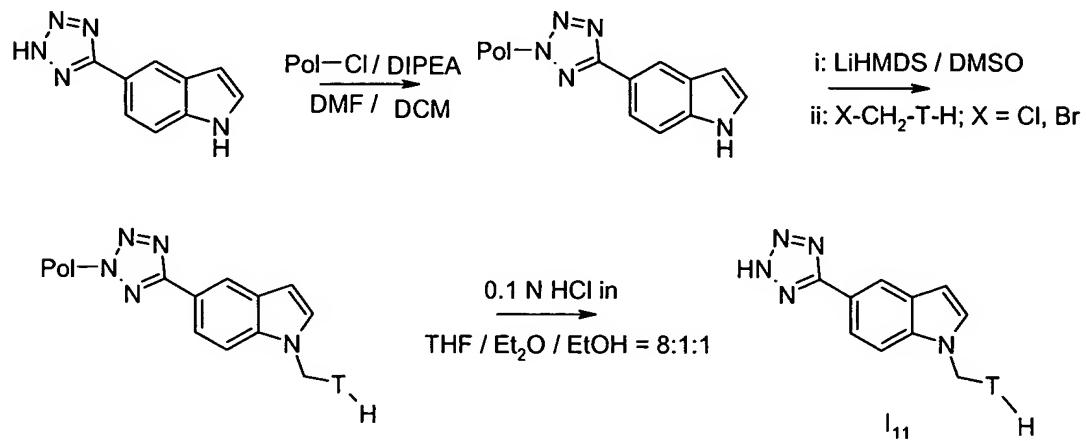
HPLC-MS (Method C): m/z: 233 (M+1); Rt = 4.24 min.

25

1-Benzyl-4-(2*H*-tetrazol-5-yl)-1*H*-indole was prepared from 1-benzyl-1*H*-indole-4-carbonitrile according to the method described in example 594.

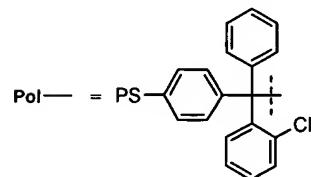
HPLC-MS (Method C): m/z: 276 (M+1); Rt = 3.44 min.

General procedure (L) for preparation of compounds of general formula I₁₁:



wherein T is as defined above and

Pol- is a polystyrene resin loaded with a 2-chlorotriptyl linker, graphically shown below:

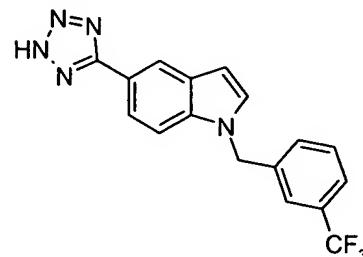


10

This general procedure (L) is further illustrated by the following example:

Example 812 (General procedure (L)).

5-(2H-Tetrazol-5-yl)-1-[3-(trifluoromethyl)benzyl]-1H-indole



15

2-Chlorotriptylchloride resin (100 mg, 0.114 mmol active chloride) was swelled in dichloromethane (2 mL) for 30 min. The solvent was drained, and a solution of 5-(2H-

tetrazol-5-yl)-1*H*-indole (example 810) (63 mg, 0.34 mmol) in a mixture of *N,N*-dimethylformamide, dichloromethane and *N,N*-di(2-propyl)ethylamine (DIPEA) (5:5:2) (1.1 mL) was added. The reaction mixture was shaken at room temperature for 20 hours. The solvent was removed by filtration, and the resin was washed consecutively with *N,N*-dimethylformamide (2 x 4 mL), dichloromethane (6 x 4 mL) and methyl sulfoxide (2 x 4 mL).
5 Methyl sulfoxide (1 mL) was added, followed by the addition of a solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 0.57 mL, 0.57 mmol). The mixture was shaken for 30 min at room temperature, before 3-(trifluoromethyl)benzyl bromide (273 mg, 1.14 mmol) was added as a solution in methyl sulfoxide (0.2 mL). The reaction mixture was
10 shaken for 20 hours at room temperature. The drained resin was washed consecutively with methyl sulfoxide (2 x 4 mL), dichloromethane (2 x 4 mL), methanol (2 x 4 mL), dichloromethane (2 x 4 mL) and tetrahydrofuran (4 mL). The resin was treated with a solution of hydrogen chloride in tetrahydrofuran, ethyl ether and ethanol = 8:1:1 (0.1 M, 3 mL) for 6 hours at room temperature. The resin was drained and the filtrate was concentrated *in*
15 *vacuo*. The crude product was re-suspended in dichloromethane (1.5 mL) and concentrated three times to afford the title compound (35 mg). No further purification was necessary.

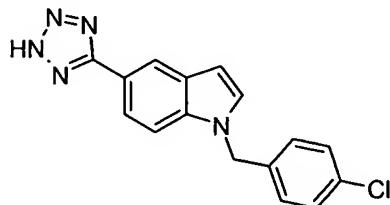
HPLC-MS (Method B): m/z: 344 (M+1); Rt = 4.35 min.

¹H-NMR (DMSO-*d*₆): δ 8.29 (1H, s), 7.80 (1H, dd), 7.72 (2H, m), 7.64 (2H, bs), 7.56 (1H, t),
20 7.48 (1H, d), 6.70 (1H, d), 5.62 (2H, s).

The compounds in the following examples were prepared in a similar fashion. Optionally, the compounds can be further purified by recrystallization or by chromatography.

25 Example 813 (General procedure (L)).

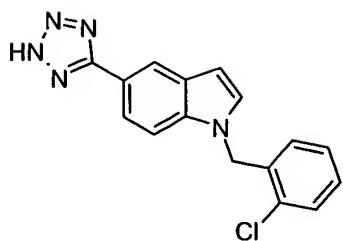
1-(4-Chlorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 310 (M+1); Rt = 4.11 min.

30 Example 814 (General procedure (L)).

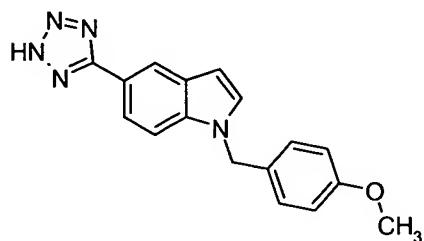
1-(2-Chlorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 310 (M+1); Rt = 4.05 min.

Example 815 (General procedure (L)).

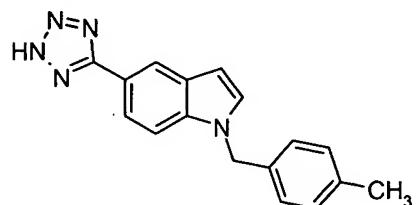
- 5 1-(4-Methoxybenzyl)-5-(2H-tetrazol-5-yl)-1H-indole



HPLC-MS (Method B): m/z: 306 (M+1); Rt = 3.68 min.

Example 816 (General procedure (L)).

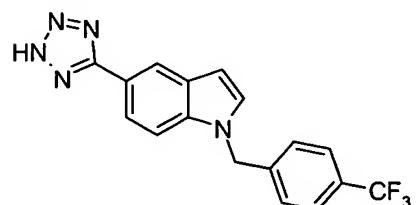
- 10 1-(4-Methylbenzyl)-5-(2H-tetrazol-5-yl)-1H-indole



HPLC-MS (Method B): m/z: 290 (M+1); Rt = 3.98 min.

Example 817 (General procedure (L)).

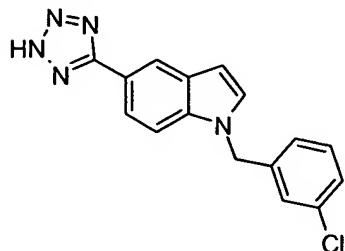
- 15 5-(2H-Tetrazol-5-yl)-1-[4-(trifluoromethyl)benzyl]-1H-indole



HPLC-MS (Method B): m/z: 344 (M+1); Rt = 4.18 min.

Example 818 (General procedure (L)).

1-(3-Chlorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole

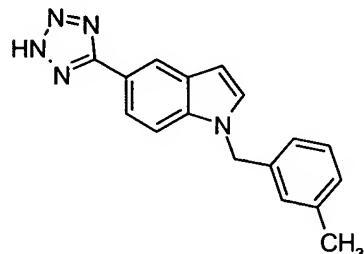


HPLC-MS (Method B): m/z: 310 (M+1); Rt = 4.01 min.

5

Example 819 (General procedure (L)).

1-(3-Methylbenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole

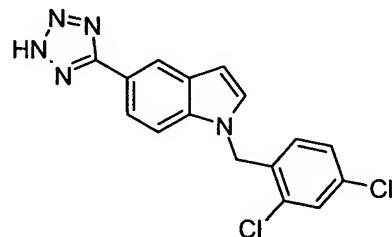


HPLC-MS (Method B): m/z: 290 (M+1); Rt = 3.98 min.

10

Example 820 (General procedure (L)).

1-(2,4-Dichlorobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole

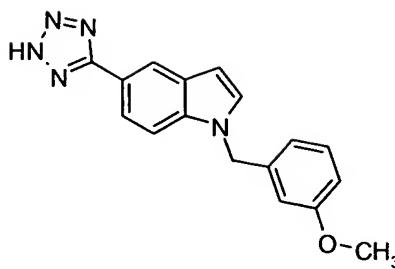


HPLC-MS (Method B): m/z: 344 (M+1); Rt = 4.41 min.

15

Example 821 (General procedure (L)).

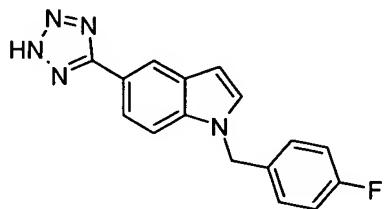
1-(3-Methoxybenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 306 (M+1); Rt = 3.64 min.

Example 822 (General procedure (L)).

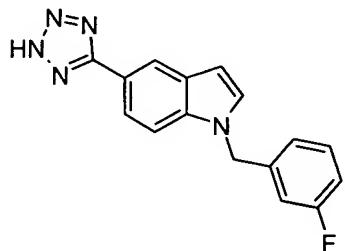
- 5 1-(4-Fluorobenzyl)-5-(2H-tetrazol-5-yl)-1H-indole



HPLC-MS (Method B): m/z: 294 (M+1); Rt = 3.71 min.

Example 823 (General procedure (L)).

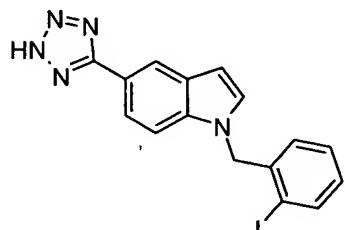
- 10 1-(3-Fluorobenzyl)-5-(2H-tetrazol-5-yl)-1H-indole



HPLC-MS (Method B): m/z: 294 (M+1); Rt = 3.68 min.

Example 824 (General procedure (L)).

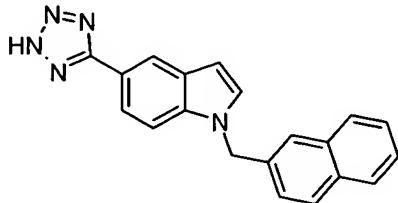
- 15 1-(2-Iodobenzyl)-5-(2H-tetrazol-5-yl)-1H-indole



HPLC-MS (Method B): m/z: 402 (M+1); Rt = 4.11 min.

Example 825 (General procedure (L)).

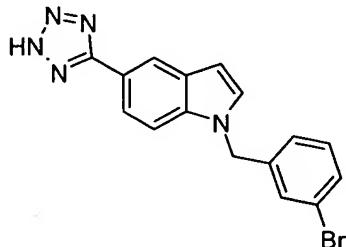
1-[(Naphthalen-2-yl)methyl]-5-(2*H*-tetrazol-5-yl)-1*H*-indole



5 HPLC-MS (Method B): m/z: 326 (M+1); Rt = 4.18 min.

Example 826 (General procedure (L)).

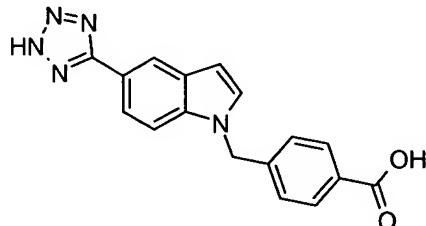
1-(3-Bromobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



10 HPLC-MS (Method B): m/z: 354 (M+1); Rt = 4.08 min.

Example 827 (General procedure (L)).

1-(4-Carboxybenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole

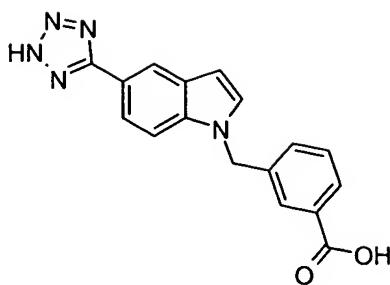


15 In this preparation, a larger excess of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 1.7 mL, 1.7 mmol) was used.

HPLC-MS (Method B): m/z: 320 (M+1); Rt = 2.84 min.

Example 828 (General procedure (L)).

20 1-(3-Carboxybenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



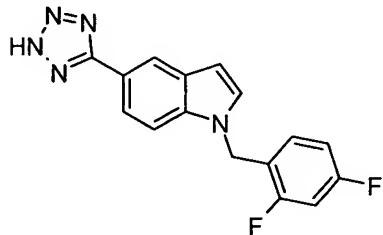
In this preparation, a larger excess of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 1.7 mL, 1.7 mmol) was used.

HPLC-MS (Method B): m/z: 320 (M+1); Rt = 2.91 min.

5

Example 829 (General procedure (L)).

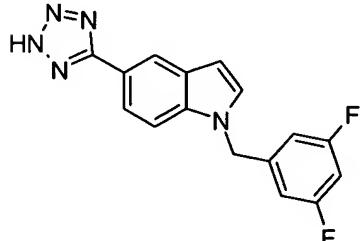
1-(2,4-Difluorobenzyl)-5-(2H-tetrazol-5-yl)-1H-indole



10 HPLC-MS (Method B): m/z: 312 (M+1); Rt = 3.78 min.

Example 830 (General procedure (L)).

1-(3,5-Difluorobenzyl)-5-(2H-tetrazol-5-yl)-1H-indole



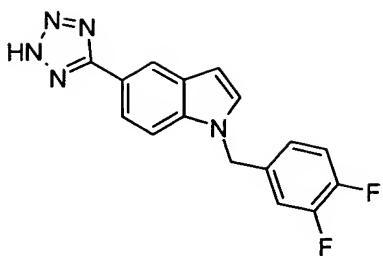
15

HPLC-MS (Method B): m/z: 312 (M+1); Rt = 3.78 min.

Example 831 (General procedure (L)).

1-(3,4-Difluorobenzyl)-5-(2H-tetrazol-5-yl)-1H-indole

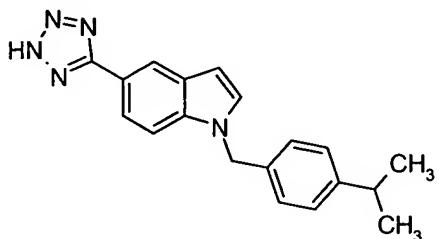
318



HPLC-MS (Method B): m/z: 312 (M+1); Rt = 3.81 min.

Example 832 (General procedure (L)).

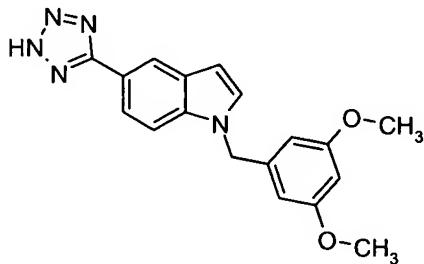
- 5 1-[4-(2-Propyl)benzyl]-5-(2H-tetrazol-5-yl)-1H-indole



HPLC-MS (Method B): m/z: 318 (M+1); Rt = 4.61 min.

Example 833 (General procedure (L)).

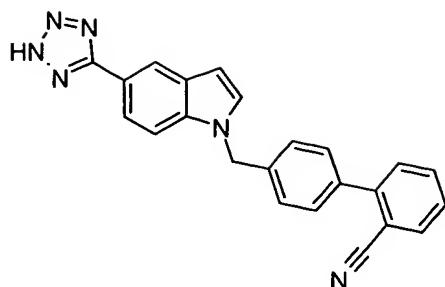
- 10 1-(3,5-Dimethoxybenzyl)-5-(2H-tetrazol-5-yl)-1H-indole



HPLC-MS (Method B): m/z: 336 (M+1); Rt = 3.68 min.

Example 834 (General procedure (L)).

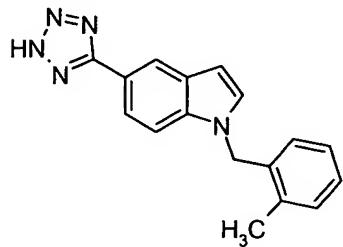
- 15 1-(2'-Cyanobiphenyl-4-ylmethyl)-5-(2H-tetrazol-5-yl)-1H-indole



HPLC-MS (Method B): m/z: 377 (M+1); Rt = 4.11 min.

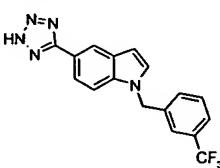
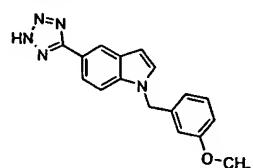
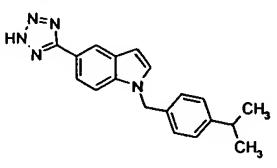
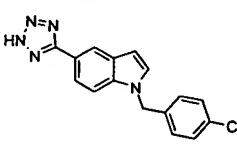
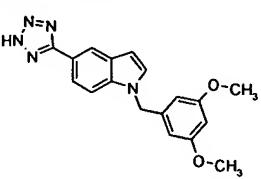
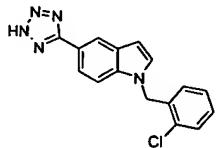
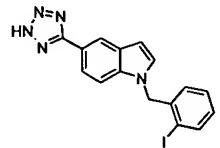
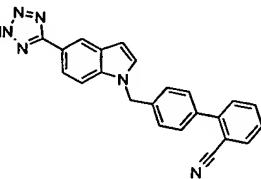
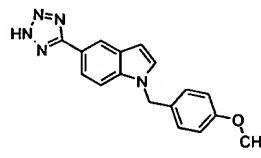
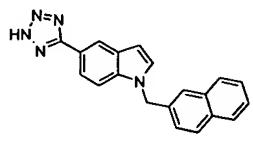
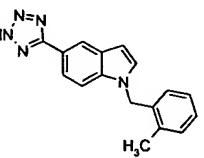
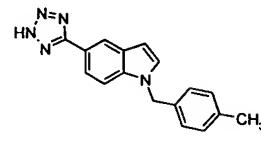
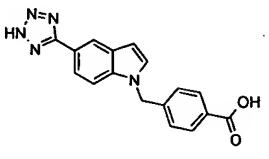
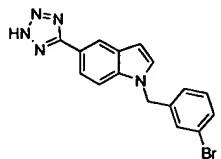
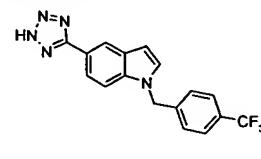
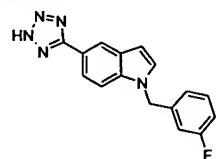
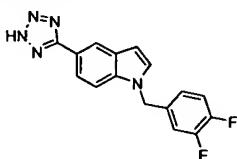
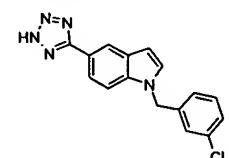
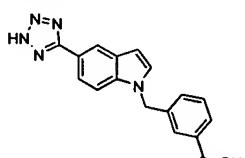
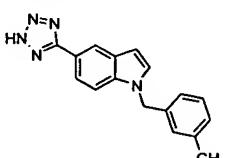
Example 835 (General procedure (L)).

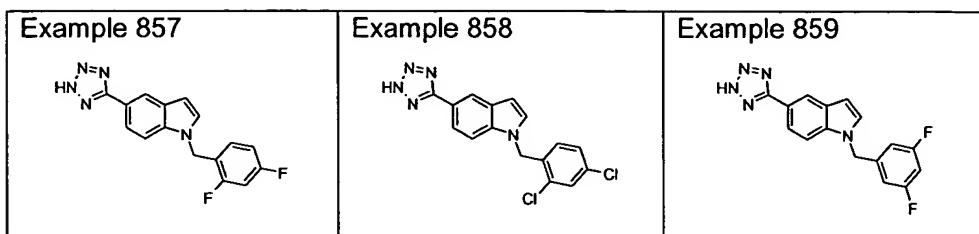
- 5 1-(2-Methylbenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



HPLC-MS (Method B): m/z: 290 (M+1); Rt = 3.98 min.

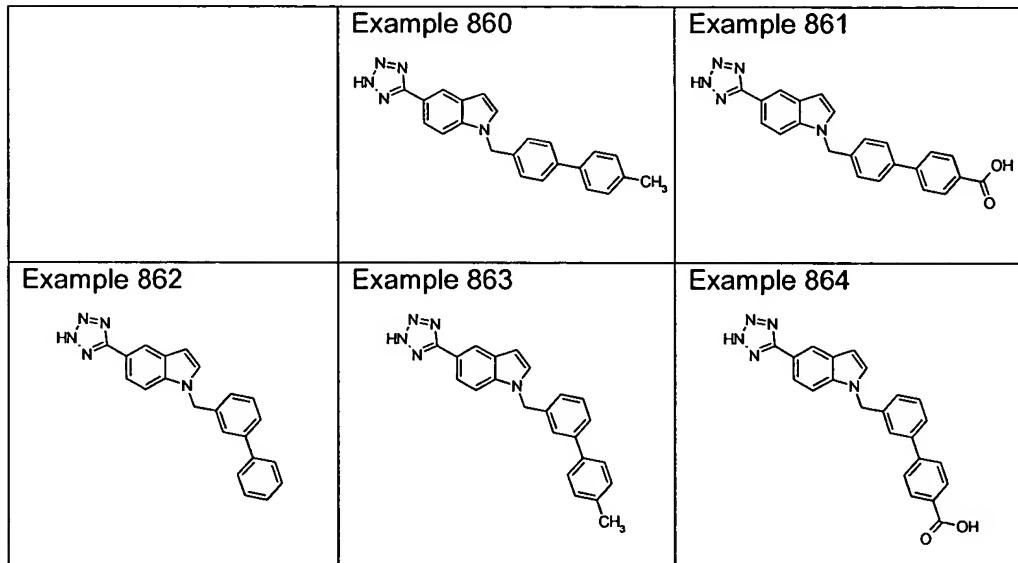
- 10 Further compounds of the invention that may be prepared according to general procedure (K) and/or (L) includes:

Example 836 	Example 837 	Example 838 
Example 839 	Example 840 	Example 841 
Example 842 	Example 843 	Example 844 
Example 845 	Example 846 	Example 847 
Example 848 	Example 849 	Example 850 
Example 851 	Example 852 	Example 853 
Example 854 	Example 855 	Example 856 

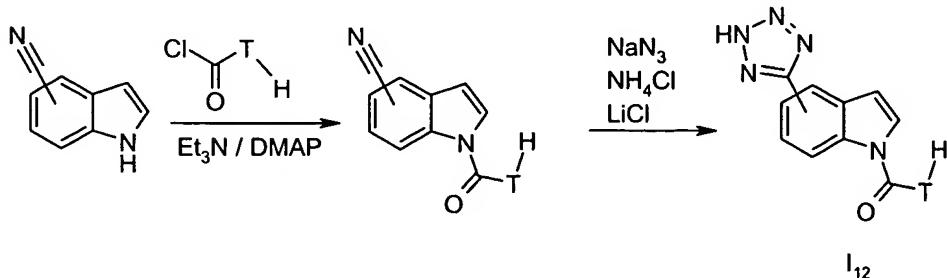


The following compounds of the invention may be prepared eg. from 1-(4-bromobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole (example 807) or from the analogue 1-(3-bromobenzyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole and aryl boronic acids via the Suzuki coupling reaction eg as

- 5 described in Littke, Dai & Fu *J. Am. Chem. Soc.*, **2000**, *122*, 4020-8 (or references cited therein), or using the methodology described in general procedure (E), optionally changing the palladium catalyst to bis(*tri-tert*-butylphosphine)palladium (0).



10 **General procedure (M) for preparation of compounds of general formula I₁₂:**

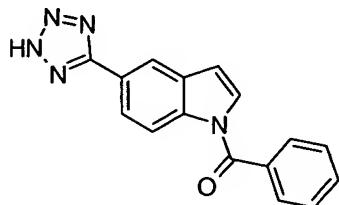


wherein T is as defined above.

The general procedure (M) is further illustrated by the following example:

Example 865 (General procedure (M)).

5 1-Benzoyl-5-(2*H*-tetrazol-5-yl)-1*H*-indole



To a solution of 5-cyanoindole (1.0 g, 7.0 mmol) in dichloromethane (8 mL) was added 4-(dimethylamino)pyridine (0.171 g, 1.4 mmol), triethylamine (1.96 mL, 1.42 g, 14 mmol) and benzoyl chloride (0.89 mL, 1.08 g, 7.7 mmol). The resulting mixture was stirred for 18 hours
10 at room temperature. The mixture was diluted with dichloromethane (80 mL) and washed consecutively with a saturated solution of sodium hydrogencarbonate (40 mL) and brine (40 mL). The organic phase was dried with magnesium sulfate (1 hour). Filtration and concentration furnished the crude material which was purified by flash chromatography on silica gel, eluting with ethyl acetate/heptanes = 2:3. 1-Benzoyl-1*H*-indole-5-carbonitrile was
15 obtained as a solid.

HPLC-MS (Method C): m/z: 247 (M+1); Rt = 4.07 min.

1-Benzoyl-1*H*-indole-5-carbonitrile was transformed into 1-benzoyl-5-(2*H*-tetrazol-5-yl)-1*H*-indole by the method described in example 594.
20

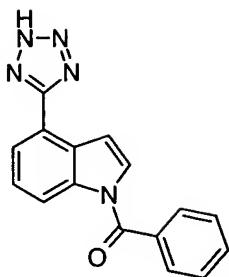
HPLC (Method C): Rt = 1.68 min.

25 The compound in the following example was prepared by the same procedure.

Example 866 (General procedure (M)).

1-Benzoyl-4-(2*H*-tetrazol-5-yl)-1*H*-indole

323



1-Benzoyl-1*H*-indole-4-carbonitrile was prepared from 4-cyanoindole according to the method described in example 865.

HPLC-MS (Method C): m/z: 247 (M+1); Rt = 4.24 min.

5

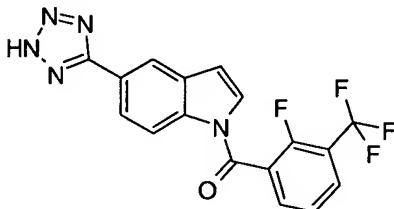
1-Benzoyl-4-(2*H*-tetrazol-5-yl)-1*H*-indole was prepared from 1-benzoyl-1*H*-indole-4-carbonitrile according to the method described in example 594.

HPLC (Method C): Rt = 1.56 min.

10

Example 867 (General procedure (M))

(2-Fluoro-3-trifluoromethylphenyl)-[5-(2*H*-tetrazol-5-yl)-indol-1-yl]-methanone

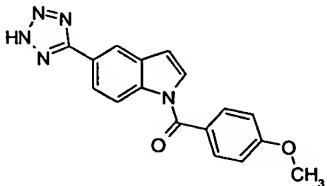


HPLC-MS (Method B): m/z = 376 (M+1); Rt = 4.32 min.

15

Example 868 (General procedure (M))

(4-Methoxyphenyl)-[5-(2*H*-tetrazol-5-yl)-indol-1-yl]-methanone

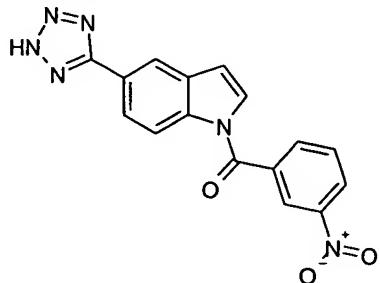


HPLC-MS (Method B): m/z = 320 (M+1); Rt = 3.70 min.

20

Example 869 (General procedure (M))

(3-Nitrophenyl)-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone

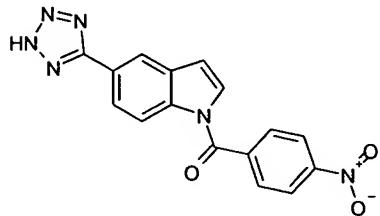


HPLC-MS (Method B): m/z = 335 (M+1); Rt = 3.72 min.

5

Example 870 (General procedure (M))

(4-Nitrophenyl)-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone

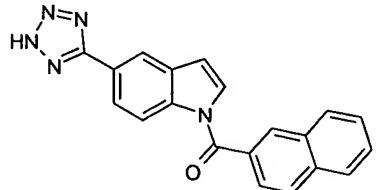


HPLC-MS (Method B): m/z = 335 (M+1); Rt = 3.71 min.

10

Example 871 (General procedure (M))

Naphthalen-2-yl-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone



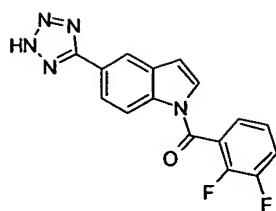
HPLC-MS (Method C): m/z = 340 (M+1); Rt = 4.25 min.

15

Example 872 (General procedure (M))

(2,3-Difluorophenyl)-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone

325



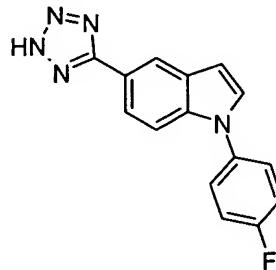
HPLC-MS (Method B: m/z = 326 (M+1); Rt = 3.85 min.

The following known and commercially available compounds do all bind to the His B10 Zn²⁺

5 site of the insulin hexamer:

Example 873

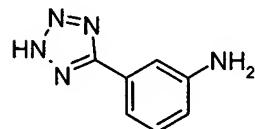
1-(4-Fluorophenyl)-5-(2*H*-tetrazol-5-yl)-1*H*-indole



10

Example 874

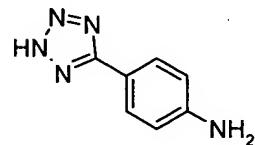
1-Amino-3-(2*H*-tetrazol-5-yl)benzene



15

Example 875

1-Amino-4-(2*H*-tetrazol-5-yl)benzene



20

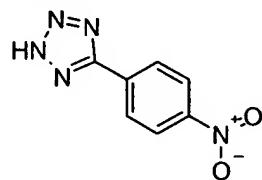
A mixture of 4-aminobenzonitrile (10 g, 84.6 mmol), sodium azide (16.5 g, 254 mmol) and ammonium chloride (13.6 g, 254 mmol) in DMF was heated at 125 °C for 16 hours. The cooled mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was added water (200 mL) and diethyl ether (200 mL) which resulted in crystallisation. The 5 mixture was filtered and the solid was dried *in vacuo* at 40 °C for 16 hours to afford 5-(4-aminophenyl)-2*H*-tetrazole.

¹H NMR DMSO-*d*₆): δ = 5.7 (3H, bs), 6.69 (2H, d), 7.69 (2H, d).

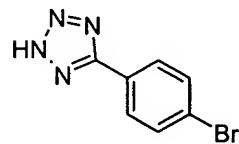
HPLC-MS (Method C): m/z: 162 (M+1); Rt = 0,55 min.

10

Example 8761-Nitro-4-(2*H*-tetrazol-5-yl)benzene

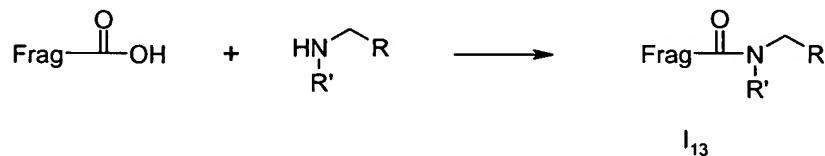


Example 8771-Bromo-4-(2*H*-tetrazol-5-yl)benzene



15

General procedure (N) for solution phase preparation of amides of general formula I₁₃:



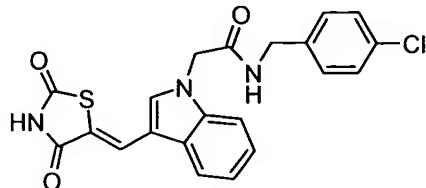
20 wherein Frag is any fragment carrying a carboxylic acid group, R is hydrogen, optionally substituted aryl or C₁₋₈-alkyl and R' is hydrogen or C₁₋₄-alkyl.

Frag-CO₂H may be prepared eg by general procedure (D) or by other similar procedures described herein, or may be commercially available.

25

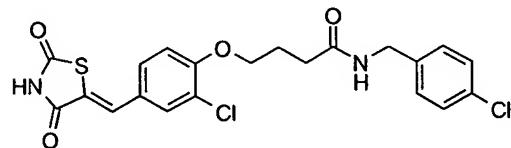
The procedure is further illustrated in the following example 878:

Example 878 (General procedure (N))

N-(4-Chlorobenzyl)-2-[3-(2,4-dioxothiazolidin-5-ylidenemethyl)-1*H*-indol-1-yl]acetamide

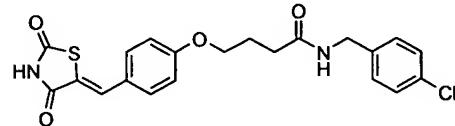
- 5 [3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indol-1-yl]acetic acid (example 478, 90.7 mg, 0.3 mmol) was dissolved in NMP (1 mL) and added to a mixture of 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide, hydrochloride (86.4 mg, 0.45 mmol) and 1-hydroxybenzotriazol (68.8 mg, 0.45 mmol) in NMP (1 mL). The resulting mixture was shaken at RT for 2 h. 4-Chlorobenzylamine (51 mg, 0.36 mmol) and DIPEA (46.4 mg, 0.36 mmol) in NMP (1 mL)
- 10 were added to the mixture and the resulting mixture shaken at RT for 2 days. Subsequently ethyl acetate (10 mL) was added and the resulting mixture washed with 2x10 mL water followed by saturated ammonium chloride (5 mL). The organic phase was evaporated to dryness giving 75 mg (57%) of the title compound.
- 15 HPLC-MS (Method C): m/z: 426 (M+1); Rt. = 3.79 min.

Example 879 (General procedure (N))

N-(4-Chlorobenzyl)-4-[2-chloro-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyramide

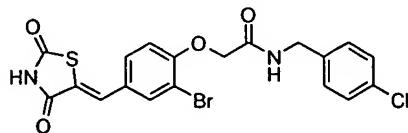
- 20 HPLC-MS (Method A): m/z: 465 (M+1); Rt = 4.35 min.

Example 880 (General procedure (N))

N-(4-Chlorobenzyl)-4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyramide

- 25 HPLC-MS (Method A): m/z: 431 (M+1); Rt = 3.68 min.

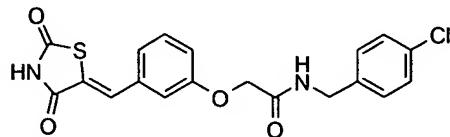
Example 881 (General procedure (N))

N-(4-Chlorobenzyl)-2-[2-bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]acetamide

HPLC-MS (Method A): m/z: 483 (M+1); Rt = 4.06 min.

5

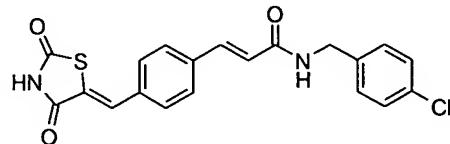
Example 882 (General procedure (N))

N-(4-Chlorobenzyl)-2-[3-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]acetamide

HPLC-MS (Method A): m/z: 403 (M+1); Rt = 4.03 min.

10

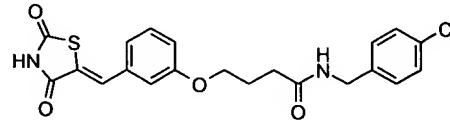
Example 883 (General procedure (N))

N-(4-Chlorobenzyl)-3-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenyl]acrylamide

HPLC-MS (Method A): m/z: 399 (M+1); Rt = 3.82.

15

Example 884 (General procedure (N))

N-(4-Chlorobenzyl)-4-[3-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyramide

HPLC-MS (Method A): m/z: 431 (M+1); Rt = 3.84 min.

20

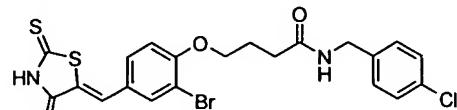
Example 885 (General procedure (N))

N-(4-Chlorobenzyl)-4-[2-bromo-4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenoxy]butyramide

HPLC-MS (Method A): m/z: 511 (M+1); Rt = 4.05 min.

Example 886 (General procedure (N))

4-[2-Bromo-4-(4-oxo-2-thioxothiazolidin-5-ylidenemethyl)-phenoxy]-N-(4-chlorobenzyl)-butyramide

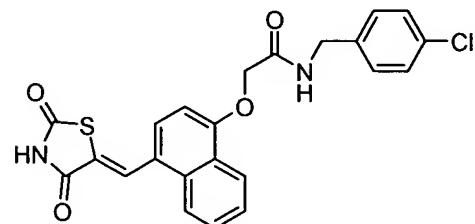


5

HPLC-MS (Method A): m/z: 527 (M+1); Rt = 4.77 min.

Example 887 (General procedure (N))

N-(4-Chlorobenzyl)-2-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]acetamide

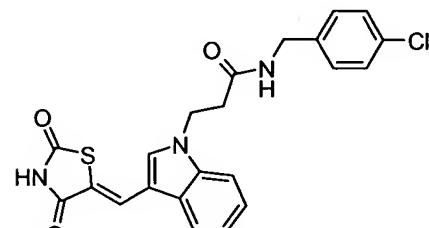


10

HPLC-MS (Method C): m/z: 431 (M+1); Rt. = 4.03 min.

Example 888 (General procedure (N))

N-(4-Chlorobenzyl)-3-[3-(2,4-dioxothiazolidin-5-ylidenemethyl)-1H-indol-1-yl]propionamide

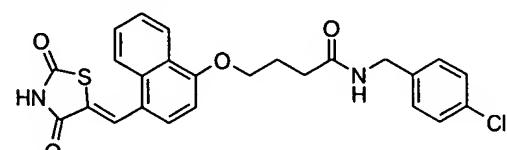


15

HPLC-MS (Method C): m/z: 440 (M+1); Rt. = 3.57 min.

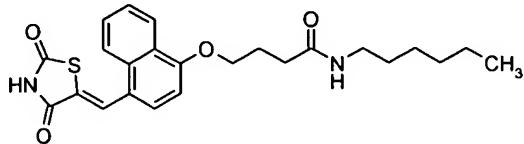
Example 889 (General procedure (N))

N-(4-Chlorobenzyl)-4-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)naphthalen-1-yloxy]butyramide

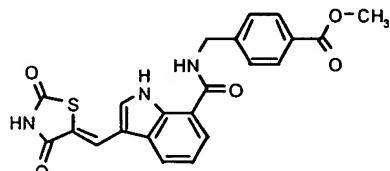


20

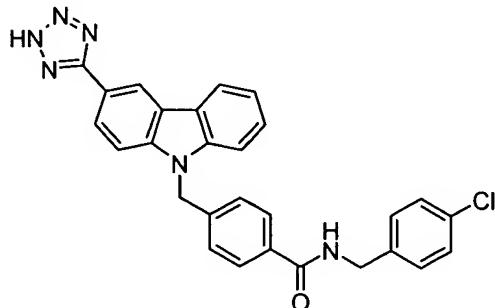
HPLC-MS (Method C): m/z: 481 (M+1); Rt = 4.08 min.

Example 890 (General procedure (N))**4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-N-hexylbutyramide**

- 5 HPLC-MS (Method C): m/z: 441 (M+1); Rt = 4.31 min.

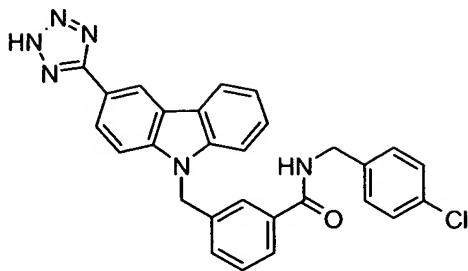
Example 891 (General Procedure (N))**4-((3-(2,4-Dioxothiazolidin-5-ylidenemethyl)indole-7-carbonyl)amino)methylbenzoic acid methyl ester**

- 10 HPLC-MS (Method C): m/z: 436 (M+1); Rt.= 3.55 min.

Example 892 (General procedure (N))**N-(4-Chlorobenzyl)-4-[3-(2*H*-tetrazol-5-yl)carbazol-9-ylmethyl]benzamide**

- 15 HPLC-MS (Method C): m/z:493 (M+1); Rt = 4.19 min.

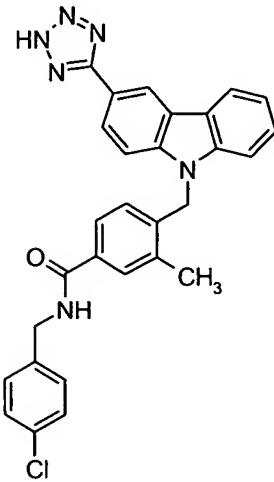
Example 893 (General procedure (N))**N-(4-Chlorobenzyl)-3-[3-(2*H*-tetrazol-5-yl)carbazol-9-ylmethyl]benzamide**



HPLC-MS (Method C): m/z: 493 (M+1); Rt = 4.20 min.

Example 894 (General Procedure (N))

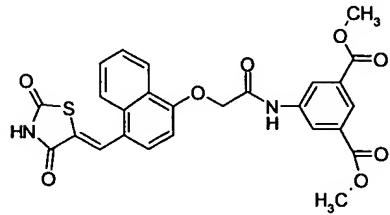
- 5 *N*-(4-Chlorobenzyl)-3-methyl-4-[3-(2*H*-tetrazol-5-yl)-carbazol-9-ylmethyl]benzamide



HPLC-MS (Method C): m/z: 507 (M+1); Rt = 4.37min.

Example 895 (General procedure (N))

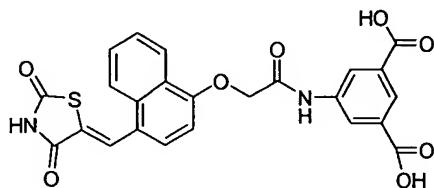
- 10 5-{2-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-acetylamo}-isophthalic acid dimethyl ester



HPLC-MS (Method C): m/z = 521 (M+1); Rt. = 4.57 min.

- 15 Example 896 (General procedure (N))

5-{2-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-acetylamo}-isophthalic acid

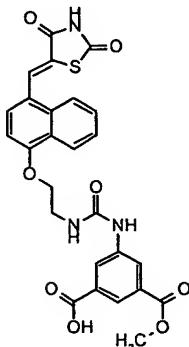


HPLC-MS (Method C): m/z = 515 (M+23); Rt. = 3.09 min.

5

Example 897 (General procedure (N))

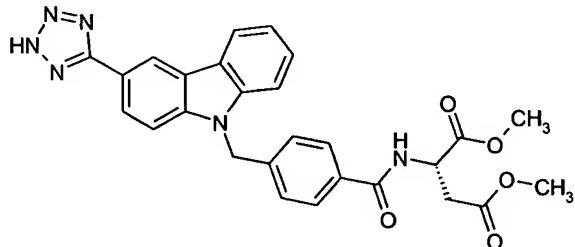
5-(3-{2-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-ethyl}-ureido)-isophthalic acid monomethyl ester



10 HPLC-MS (Method C): m/z = 536 (M+1); Rt = 3,58 min.

Example 898 (General Procedure (N)).

2-{4-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}succinic acid dimethyl ester



15 4-[3-(1H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoic acid (2.00 g, 5.41 mmol), 1-hydroxybenzotriazole (1.46 g, 10.8 mmol) and N,N-di(2-propyl)ethylamine (4.72 mL, 3.50 g, 27.1 mmol) were dissolved in dry N,N-dimethylformamide (60 mL). The mixture was cooled in an ice-water bath, and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.45 g, 7.56 mmol) and (S)-aminosuccinic acid dimethyl ester hydrochloride (1.28 g, 6.48

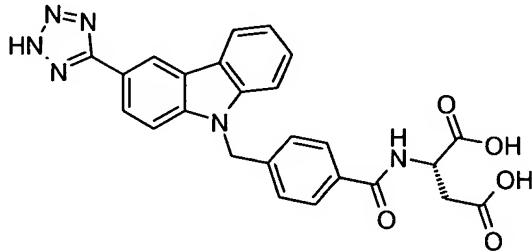
mmol) were added. The cooling was discontinued, and the reaction mixture was stirred at room temperature for 18 hours before it was poured into hydrochloric acid (0.1 N, 600 mL). The solid was collected by filtration and washed with water (2 X 25 mL) to furnish the title compound.

5 HPLC-MS (Method C): m/z: 513 (M+1); Rt = 3.65 min.

$^1\text{H-NMR}$ (DMSO-d₆): δ 8.90 (1H, d), 8.86 (1H, d), 8.29 (1H, d), 8.11 (1H, dd), 7.87 (1H, d), 7.75 (2H, d), 7.69 (1H, d), 7.51 (1H, t), 7.32 (1H, t), 7.28 (2H, d), 5.82 (2H, s), 4.79 (1H, m), 3.61 (3H, s), 3.58 (3H, s), 2.92 (1H, dd), 2.78 (1H, dd).

10 Example 899 (General Procedure (N)).

2-{4-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}succinic acid



2-{4-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}succinic acid dimethyl ester (1.20 g, 2.34 mmol) was dissolved in tetrahydrofuran (30 mL). Aqueous sodium hydroxide (1

15 N, 14 mL) was added, and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was poured into hydrochloric acid (0.1 N, 500 mL). The solid was collected by filtration and washed with water (2 X 25 mL) and diethyl ether (2 X 25 mL) to furnish the title compound.

HPLC-MS (Method C): m/z: 485 (M+1); Rt = 2.94 min.

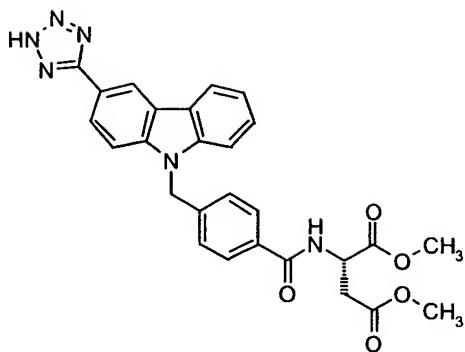
20 $^1\text{H-NMR}$ (DMSO-d₆): δ 12.44 (2H, s (br)), 8.90 (1H, d), 8.68 (1H, d), 8.29 (1H, d), 8.11 (1H, dd), 7.87 (1H, d), 7.75 (2H, d), 7.68 (1H, d), 7.52 (1H, t), 7.32 (1H, t), 7.27 (2H, d), 5.82 (2H, s), 4.70 (1H, m), 2.81 (1H, dd), 2.65 (1H, dd).

The compounds in the following examples were prepared in a similar fashion.

25

Example 900 (General procedure (N))

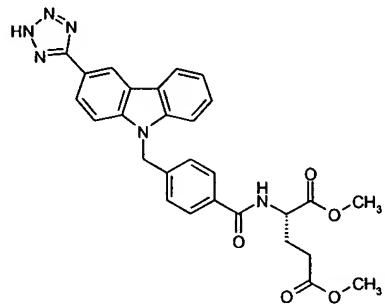
2-{4-[3-(2H-Tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoylamino}-succinic acid dimethyl ester



HPLC-MS (Method C): m/z = 513 (M+1); Rt = 3.65min.

Example 901 (General procedure (N))

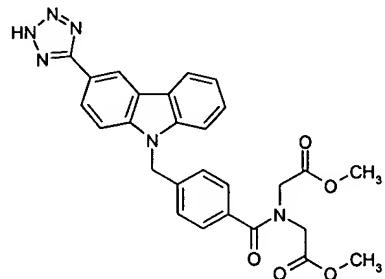
- 5 2-{4-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}pentanedioic acid dimethyl ester



HPLC-MS (Method C): m/z = 527 (M+1); Rt = 3.57min.

Example 902 (General procedure (N))

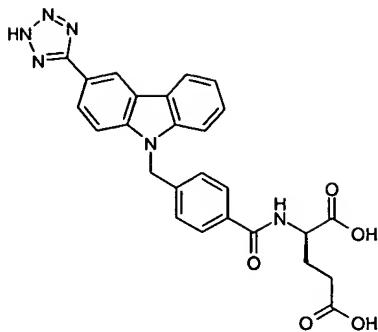
- 10 (Methoxycarbonylmethyl-{4-[3-(2H-tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoyl}-amino)-acetic acid methyl ester



HPLC-MS (Method C): m/z = 513 (M+1); Rt = 3.55min.

- 15 Example 903 (General procedure (N))

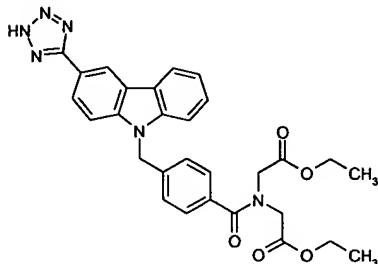
2-{4-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}pentanedioic acid



HPLC-MS (Method C): m/z = 499 (M+1); Rt = 2.87min.

Example 904 (General procedure (N))

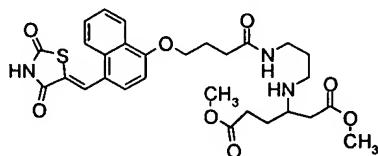
- 5 (Ethoxycarbonylmethyl-{4-[3-(2H-tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoyl}-amino)-acetic acid ethyl ester



HPLC-MS (Method C): m/z = 541 (M+1); Rt = 3.91min.

10 Example 905 (General procedure (N))

- 3-(3-{4-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-butyrylamino}-propylamino)-hexanedioic acid dimethyl ester

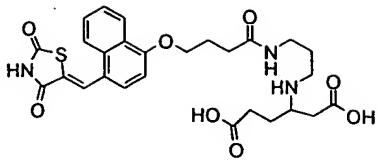


HPLC-MS (Method C: m/z = 585 (M+1); Rt = 2.81 min.

15

Example 906 (General procedure (N))

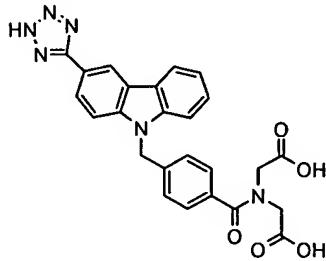
- 3-(3-{4-[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-butyrylamino}-propylamino)-hexanedioic acid



HPLC-MS (Method C): m/z = 554 (M-3); Rt = 3.19 min.

Example 907 (General procedure (N))

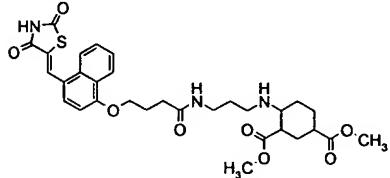
- 5 (Carboxymethyl-{4-[3-(2H-tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoyl}-amino)-acetic acid



HPLC-MS (Method C): m/z = 485 (M+1); Rt = 3.04 min.

Example 908 (General procedure (N))

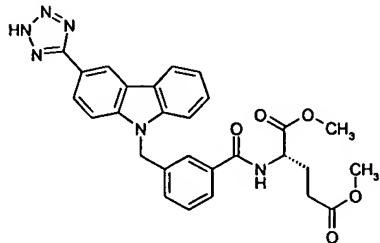
- 10 4-(3-{4-[4-(2,4-Dioxothiazolidin-5-ylidenemethyl)-naphthalen-1-yloxy]-butyrylamino}-propylamino)-cyclohexane-1,3-dicarboxylic acid dimethyl ester



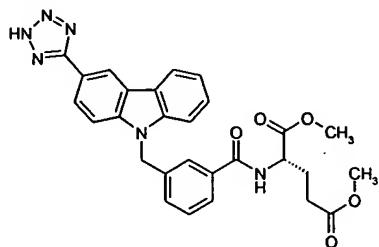
HPLC-MS (Method C): m/z = 612 (M+1); Rt = 3.24 min.

- 15 Example 909 (General procedure (N))

2-{3-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}pentanedioic acid dimethyl ester

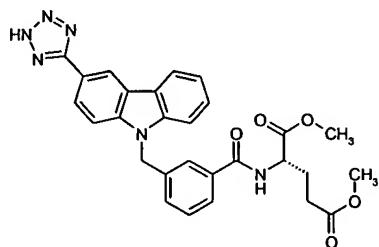


HPLC-MS (Method C): m/z = 527 (M+1); Rt = 3.65min.

Example 910 (General procedure (N))**2-{3-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}pentanedioic acid dimethyl ester**

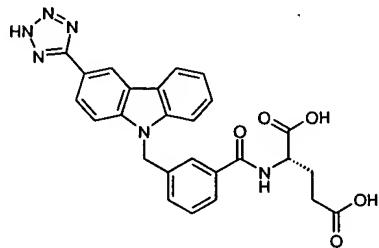
HPLC-MS (Method C): m/z = 527 (M+1); Rt = 3.65min.

5

Example 911 (General procedure (N))**2-{3-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}pentanedioic acid dimethyl ester**

HPLC-MS (Method C): m/z = 527 (M+1); Rt = 3.65min.

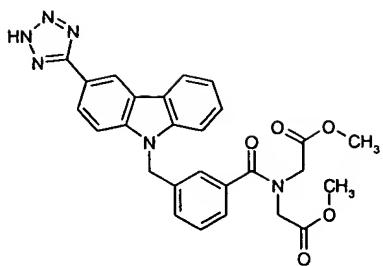
10

Example 912 (General procedure (N))**2-{3-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}pentanedioic acid**

HPLC-MS (Method C): m/z = 499 (M+1); Rt = 3.00 min.

15

Example 913 (General procedure (N))**(Methoxycarbonylmethyl-{3-[3-(2H-tetrazol-5-yl)carbazol-9-ylmethyl]benzoyl}amino)acetic acid methyl ester**

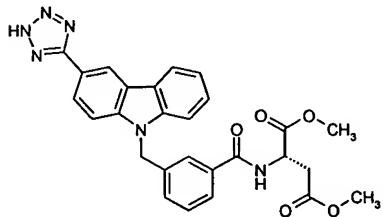


¹H-NMR (DMSO-d₆): δ 8.88 (1H, d), 8.29 (1H, d), 8.10 (1H, dd), 7.85 (1H, d), 7.67 (1H, d), 7.52 (1H, t), 7.39 (1H, t), 7.30 (2H, m), 7.17 (2H, m), 5.79 (2H, s), 4.17 (2H, s), 4.02 (2H, s), 3.62 (3H, s), 3.49 (3H, s).

5

Example 914 (General procedure (N))

2-{3-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}succinic acid dimethyl ester

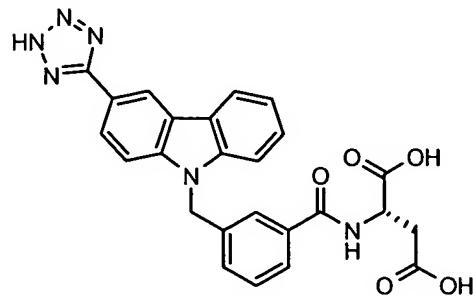


HPLC-MS (Method C): m/z = 513 (M+1); Rt = 3.70 min.

10

Example 915 (General procedure (N))

2-{3-[3-(2H-Tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoylamino}-succinic acid

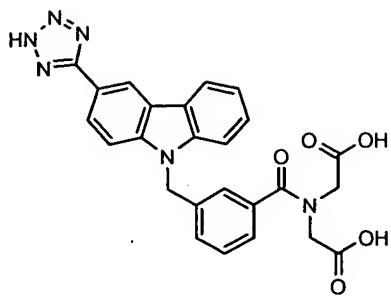


HPLC-MS (Method C): m/z = 485 (M+1); Rt = 2.96 min.

15

Example 916 (General procedure (N))

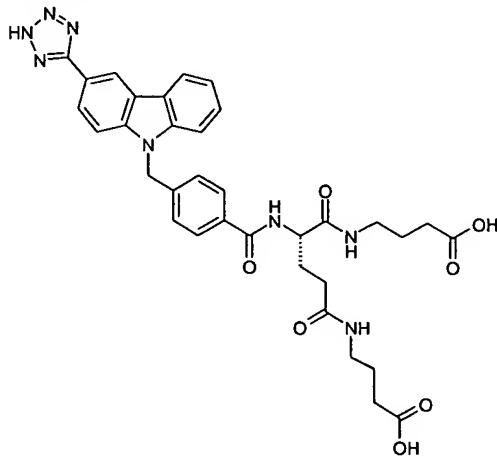
(Carboxymethyl-{3-[3-(2H-tetrazol-5-yl)carbazol-9-ylmethyl]benzoyl}amino)acetic acid



HPLC-MS (Method C): m/z = 485 (M+1); Rt = 2.87 min.

Example 917 (General procedure (N))

- 5 4-(4-(3-Carboxy-propylcarbamoyl)4-{4-[3-(2H-tetrazol-5-yl)carbazol-9-ylmethyl]-benzoylamino}butyrylamino)-butyric acid



- The title compound was prepared by coupling of (S)-2-{4-[3-(2H-tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}pentanedioic acid bis-(2,5-dioxopyrrolidin-1-yl) ester (prepared from 10 (S)-2-{4-[3-(2H-tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}pentanedioic acid by essentially the same procedure as described for the synthesis of 4-[3-(2H-tetrazol-5-yl)carbazol-9-ylmethyl]benzoic acid 2,5-dioxopyrrolidin-1-yl ester) with 4-aminobutyric acid according to the procedure described for the preparation of 4-{4-[3-(2H-tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}butyric acid .

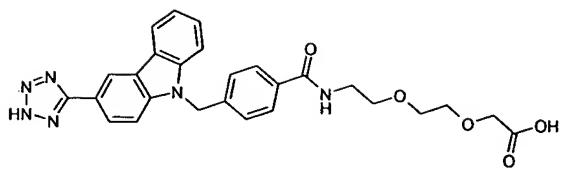
15

HPLC-MS (Method C): m/z: 669 (M+1); Rt = 2.84 min.

Example 918 (General procedure (N))

[2-(2-{4-[3-(2H-Tetrazol-5-yl)-carbazol-9-ylmethyl]benzoylamino}ethoxy)ethoxy]acetic acid

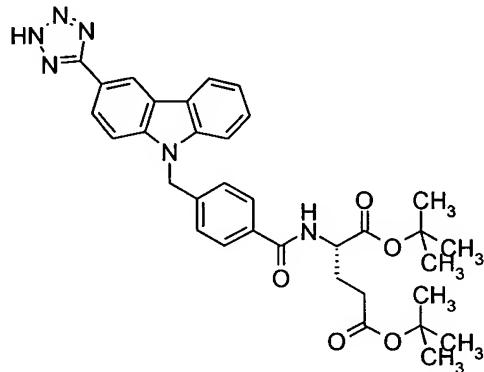
340



HPLC-MS (Method C): m/z: 515 (M+1); Rt = 3.10 min.

Example 919 (General procedure (N))

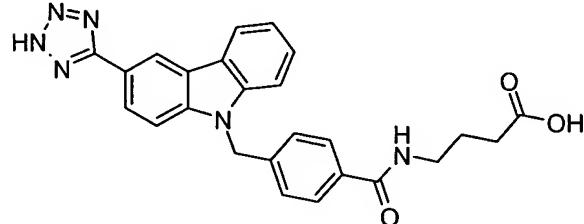
- 5 2-{4-[3-(2H-Tetrazol-5-yl)-carbazol-9-ylmethyl]-benzoylamino}-pentanedioic acid di-tert-butyl ester



HPLC-MS (Method C): m/z = 611 (M+1); Rt = 4.64 min.

- 10 Example 920 (General Procedure (N)).

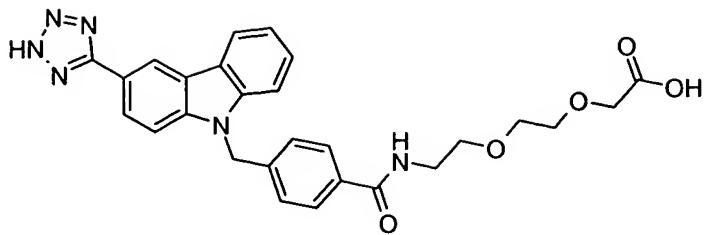
4-{4-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}butyric Acid



HPLC-MS (Method C): m/z: 455 (M+1); Rt = 3.13 min.

- 15 Example 921 (General Procedure (N)).

[2-(2-{4-[3-(2H-Tetrazol-5-yl)carbazol-9-ylmethyl]benzoylamino}ethoxy)ethoxy]acetic acid



The title compound was prepared by coupling of 4-[3-(2H-tetrazol-5-yl)carbazol-9-ylmethyl]benzoic acid 2,5-dioxopyrrolidin-1-yl ester with [2-(2-aminoethoxy)ethoxy]acetic acid (prepared from [2-[2-(Fmoc-amino)ethoxy]ethoxy]acetic acid by treatment with PS-Trisamine resin in DMF).

HPLC-MS (Method C): m/z: 515 (M+1); Rt = 3.10 min.

The commercially available compounds in the following examples do all bind to the HisB10 Zn²⁺site:

10

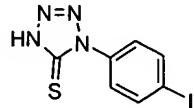
Example 922

1-(4-Bromo-3-methylphenyl)-1,4-dihydrotetrazole-5-thione



15 Example 923

1-(4-Iodophenyl)-1,4-dihydrotetrazole-5-thione



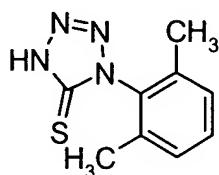
Example 924

20 1-(2,4,5-Trichlorophenyl)-1*H*-tetrazole-5-thiol



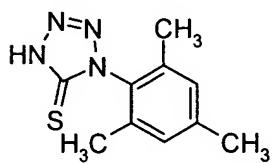
Example 925

1-(2,6-Dimethylphenyl)-1,4-dihydrotetrazole-5-thione

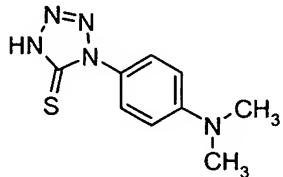


5 Example 926

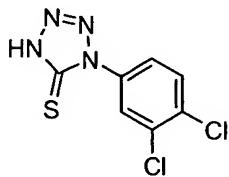
1-(2,4,6-Trimethylphenyl)-1,4-dihydrotetrazole-5-thione



Example 927

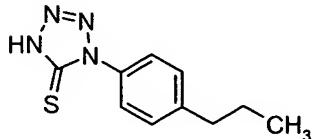
10 1-(4-Dimethylaminophenyl)-1*H*-tetrazole-5-thiol

Example 928

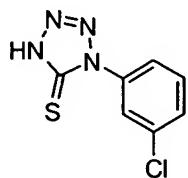
1-(3,4-Dichlorophenyl)-1,4-dihydro-1*H*-tetrazole-5-thione

15

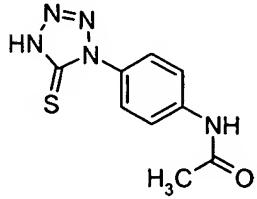
Example 929

1-(4-Propylphenyl)-1,4-dihydro-1*H*-tetrazole-5-thione

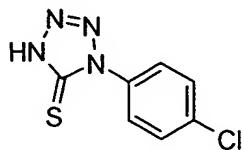
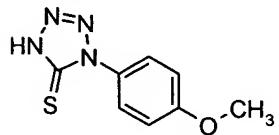
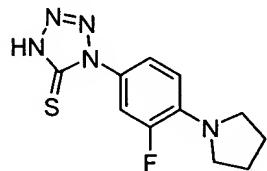
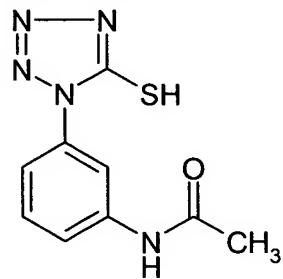
20

Example 930**1-(3-Chlorophenyl)-1,4-dihydro-1*H*-tetrazole-5-thione****5 Example 931****1-(2-Fluorophenyl)-1,4-dihydro-1*H*-tetrazole-5-thione****Example 932****10 1-(2,4-Dichlorophenyl)-1,4-dihydro-1*H*-tetrazole-5-thione****Example 933****1-(4-Trifluoromethoxyphenyl)-1,4-dihydro-1*H*-tetrazole-5-thione**

15

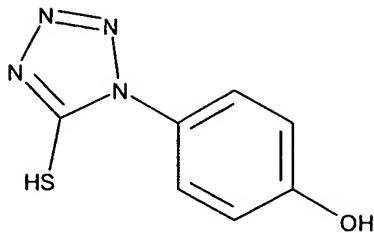
Example 934**N-[4-(5-Mercaptotetrazol-1-yl)-phenyl]-acetamide**

20

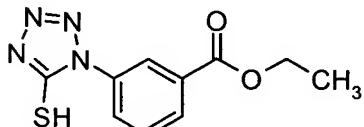
Example 935**1-(4-Chlorophenyl)-1,4-dihydrotetrazole-5-thione****5 Example 936****1-(4-Methoxyphenyl)-1,4-dihydrotetrazole-5-thione****Example 937****10 1-(3-Fluoro-4-pyrrolidin-1-ylphenyl)-1,4-dihydrotetrazole-5-thione****Example 938*****N*-[3-(5-Mercaptotetrazol-1-yl)phenyl]acetamide**

15

Example 939**1-(4-Hydroxyphenyl)-5-mercaptotetrazole**



Example 940

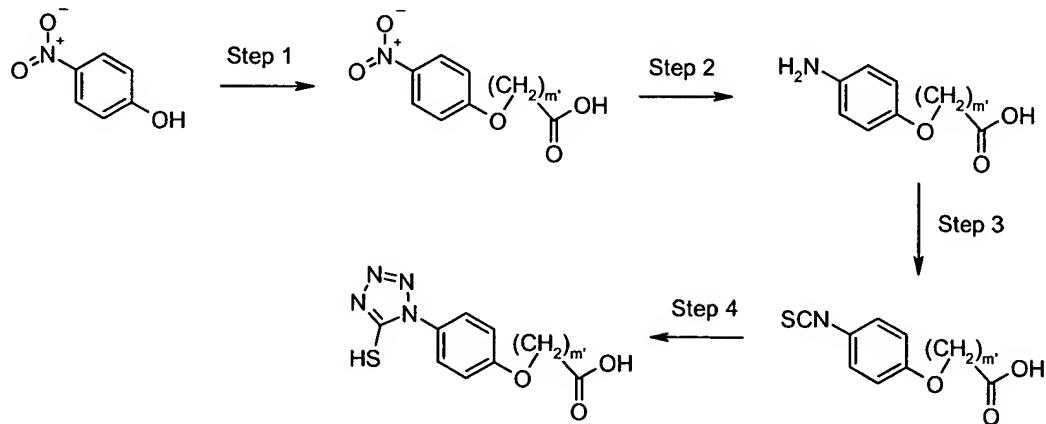


5

Preparation of 1-aryl-1,4-dihydrotetrazole-5-thiones (or the tautomeric 1-aryltetrazole-5-thiols) is described in the literature (eg. by Kauer & Sheppard, *J. Org. Chem.*, **32**, 3580-92
10 (1967)) and is generally performed eg. by reaction of aryl-isothiocyanates with sodium azide followed by acidification

1-Aryl-1,4-dihydrotetrazole-5-thiones with a carboxylic acid tethered to the aryl group may be prepared as shown in the following scheme:

15



Step 1 is a phenol alkylation and is very similar to steps 1 and 2 of general procedure (D) and may also be prepared similarly as described in example 481.

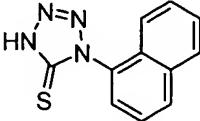
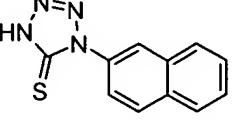
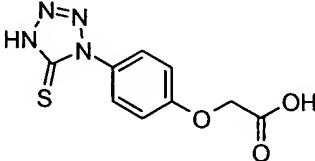
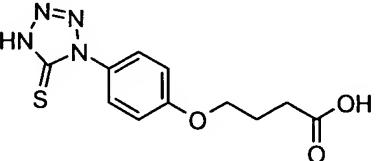
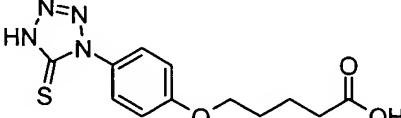
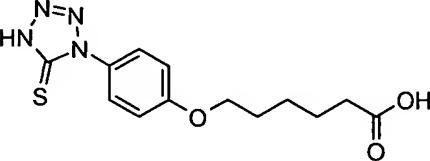
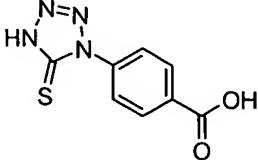
Step 2 is a reduction of the nitro group. SnCl_2 , H_2 over Pd/C and many other procedures known to those skilled in the art may be utilised.

Step 3 is formation of an arylisothiocyanate from the corresponding aniline. As reagents CS_2 ,

- 5 CSCl_2 , or other reagents known to those skilled in the art, may be utilised.

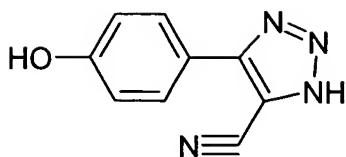
Step 4 is a conversion to mercaptotetrazole as described above.

Compounds of the invention include:

Example 941 	Example 942 
Example 943 	Example 944 
Example 945 	Example 946 
Example 947 	

Example 948

4-(4-Hydroxyphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile



Phenylsulphonyl acetonitrile (2.0 g, 11.04 mmol) was mixed with 4-hydroxybenzaldehyde (1.35 g, 11.04 mmol) in DMF (10 mL) and toluene (20 mL). The mixture was refluxed for 3 hours and subsequently evaporated to dryness *in vacuo*. The residue was treated with

- 5 diethyl ether and toluene. The solid formed was filtered to afford 2.08 g (66%) of 2-benzenesulfonyl-3-(4-hydroxyphenyl)acrylonitrile.

HPLC-MS (Method C): m/z: 286 (M+1); Rt. = 3.56 min.

A mixture of 2-benzenesulfonyl-3-(4-hydroxyphenyl)acrylonitrile (2.08 g, 7.3 mmol) and

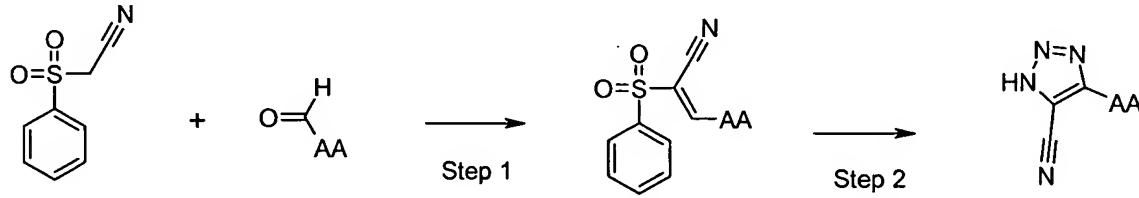
- 10 sodium azide (0.47g, 7.3 mmol) in DMF (50 mL) was heated at reflux temperature 2 hours. After cooling, the mixture was poured on ice. The mixture was evaporated in *vacuo* to almost dryness and toluene was added. After filtration, the organic phase was evaporated *in vacuo*. The residue was purified by silicagel chromatography eluting with a mixture of ethyl acetate and heptane (1:2). This afforded 1.2 g (76%) of the title compound.

15

¹H NMR (DMSO-*d*₆): 10.2 (broad,1H); 7.74 (d,2H); 6.99 (d,2H); 3.6-3.2 (broad,1H).

HPLC-MS (Method C) m/z: = 187 (M+1); Rt. = 1.93 min

General procedure (O) for preparation of compounds of general formula I₁₄:



20

wherein

AA is as defined above,

- 25 Steps 1 and 2 are described in the literature (eg Beck & Günther, *Chem. Ber.*, **106**, 2758-66 (1973))

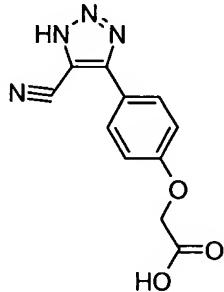
Step 1 is a Knoevenagel condensation of the aldehyde AA-CHO with phenylsulfonyl-acetonitrile and step 2 is a reaction of the vinylsulfonyl compound obtained in step 1 with sodium azide. This reaction is usually performed in DMF at 90 – 110 °C.

5

This general procedure is further illustrated in the following example 949:

Example 949 (General Procedure (O))

[4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy]acetic acid



10

Phenylsulphonylacetone (0.1 g, 0.55 mmol) was mixed with 4-formylphenoxyacetic acid (0.099 g, 0.55 mmol) in DMF (3 mL) and heated to 110 °C for 3 h and subsequently cooled to RT. Sodium azide (0.036 g, 0.55 mmol) was added and the resulting mixture was heated to 110 °C for 3 h and cooled to RT. The mixture was poured into water (20 mL) and centrifuged.

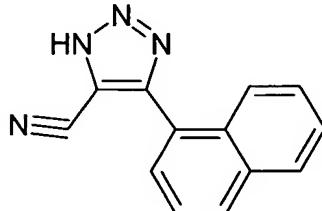
15 The supernatant was discarded, ethanol (5 mL) was added and the mixture was centrifuged again. After discarding the supernatant, the residue was dried *in vacuo* to afford 50 mg (37%) of [4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy]acetic acid.

HPLC-MS (Method C): m/z: 245 (M+1) Rt. 2.19 min.

20

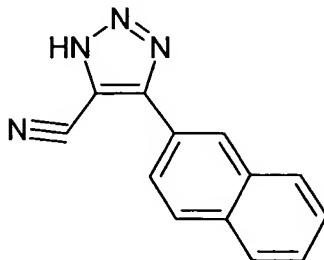
Example 950 (General Procedure (O))

5-(Naphthalen-1-yl)-3*H*-[1,2,3]triazole-4-carbonitrile



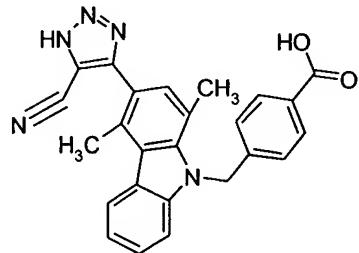
HPLC-MS (Method C): m/z: 221 (M+1); Rt. 3.43 min.

25

Example 951 (General Procedure (O))**5-(Naphthalen-2-yl)-3*H*-[1,2,3]triazole-4-carbonitrile**

HPLC-MS (Method C): m/z: 221 (M+1); Rt = 3.66 min.

5

Example 952 (General procedure (O))**4-[3-(5-Cyano-[1,2,3]triazol-4-yl)-1,4-dimethylcarbazol-9-ylmethyl]-benzoic acid**

HPLC-MS (Method C): m/z = 422 (M+1); Rt = 3.85 min.

10

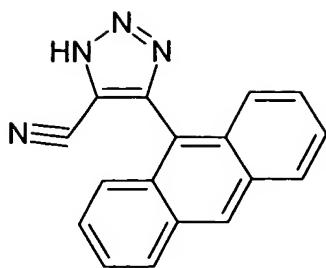
Preparation of intermediary aldehyde:

1,4 Dimethylcarbazol-3-carbaldehyde (0.68 g, 3.08 mmol) was dissolved in dry DMF (15 mL), NaH (diethyl ether washed) (0.162 g, 6.7 mol) was slowly added under nitrogen and the mixture was stirred for 1 hour at room temperature. 4-Bromomethylbenzoic acid (0.73 g, 3.4 mmol) was slowly added and the resulting slurry was heated to 40 °C for 16 hours. Water (5 mL) and hydrochloric acid (6N, 3 mL) were added. After stirring for 20 min at room temperature, the precipitate was filtered off and washed twice with acetone to afford after drying 0.38 g (34%) of 4-(3-formyl-1,4-dimethylcarbazol-9-ylmethyl)benzoic acid.

20 HPLC-MS (Method C) : m/z = 358 (M+1), RT. = 4.15 min.

Example 953 (General Procedure (O))**5-(Anthracen-9-yl)-3*H*-[1,2,3]triazole-4-carbonitrile**

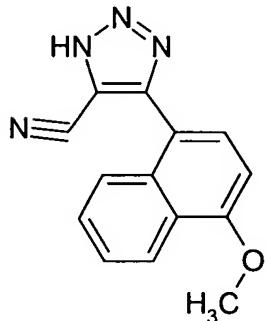
350



HPLC-MS (Method C): m/z: 271 (M+1); Rt = 3.87 min.

Example 954 (General Procedure (O))

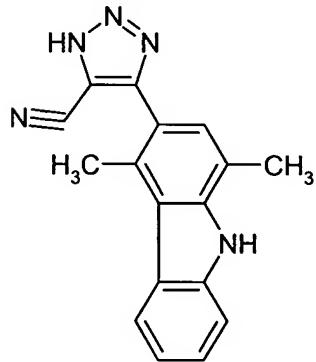
- 5 5-(4-Methoxynaphthalen-1-yl)-3H-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z: 251 (M+1); Rt = 3.57 min.

Example 955 (General Procedure (O))

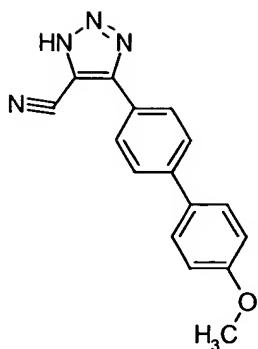
- 10 5-(1,4-Dimethyl-9H-carbazol-3-yl)-3H-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z: 288 (M+1); Rt = 3.67 min.

Example 956 (General procedure (O))

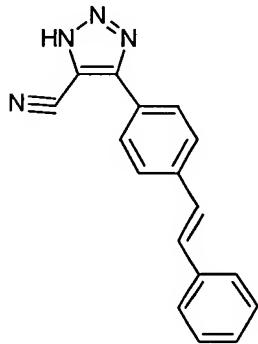
- 15 5-(4'-Methoxybiphenyl-4-yl)-3H-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z = 277 (M+1); Rt = 3.60 min.

Example 957 (General procedure (O))

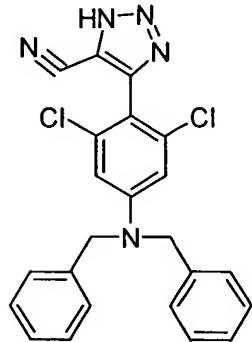
- 5 5-(4-Styrylphenyl)-3H-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z = 273 (M+1); Rt = 4.12 min.

Example 958 (General procedure (O))

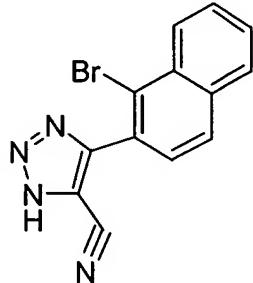
- 10 5-(2,6-Dichloro-4-dibenzylaminophenyl)-3H-[1,2,3]triazole-4-carbonitrile



HPLC-MS (Method C): m/z = 434 (M+1); Rt = 4.64 min.

Example 959 (General procedure (O))

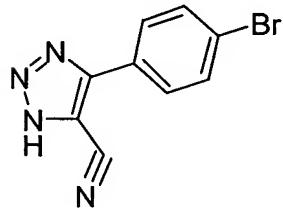
5-(1-Bromonaphthalen-2-yl)-3H-[1,2,3]triazole-4-carbonitrile



- 5 HPLC-MS (Method C: m/z = 300 (M+1); Rt. = 3.79 min.

Example 960

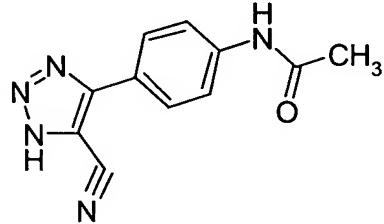
4-(4-Bromophenyl)-1H-[1,2,3]triazole-5-carbonitrile



- 10 This compound is commercially available (MENAI).

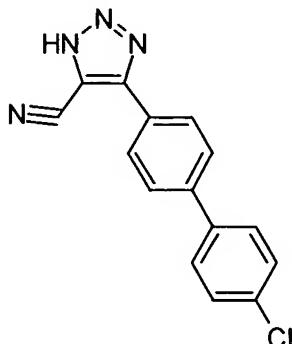
Example 961

N-[4-(5-Cyano-1H-[1,2,3]triazol-4-yl)-phenyl]-acetamide



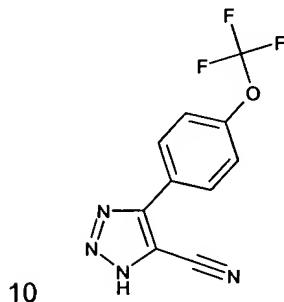
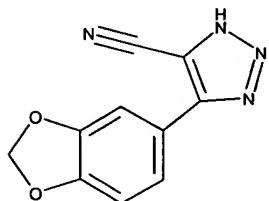
- 15 This compound is commercially available (MENAI).

Example 962 (General procedure (O))

5-(4'-Chlorobiphenyl-4-yl)-3H-[1,2,3]triazole-4-carbonitrile

HPLC-MS (Method C): m/z = 281 (M+1); Rt = 4.22 min.

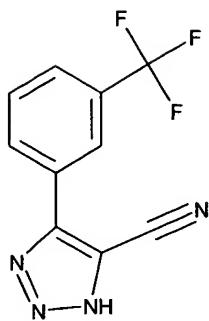
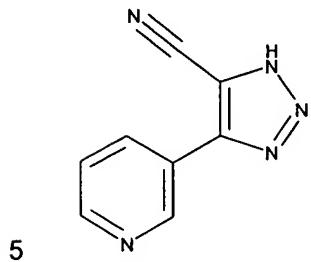
- 5 The compounds in the following examples are commercially available and may be prepared using a similar methodology:

Example 963**4-(4-Trifluoromethoxyphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile****Example 964****4-Benzo[1,3]dioxol-5-yl-1*H*-[1,2,3]triazole-5-carbonitrile**

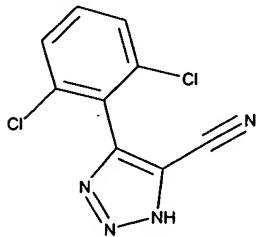
15

Example 965**4-(3-Trifluoromethylphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile**

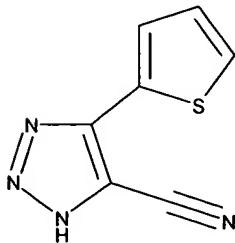
354

**Example 966****4-Pyridin-3-yl-1*H*-[1,2,3]triazole-5-carbonitrile**

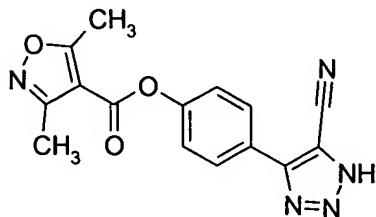
5

Example 967**4-(2,6-Dichlorophenyl)-1*H*-[1,2,3]triazole-5-carbonitrile**

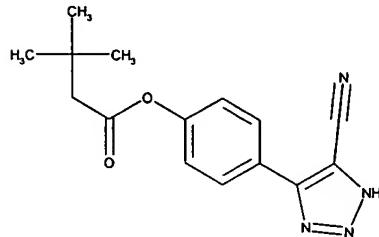
10

Example 968**4-Thiophen-2-yl-1*H*-[1,2,3]triazole-5-carbonitrile**

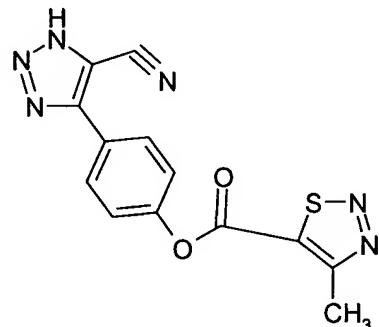
15 Example 969

3,5-Dimethylisoxazole-4-carboxylic acid 4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)phenyl ester

Example 970

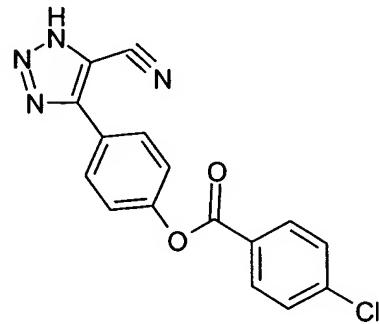
5 3,3-Dimethyl-butyric acid 4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)phenyl ester

Example 971

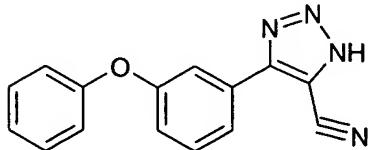
4-Methyl-[1,2,3]thiadiazole-5-carboxylic acid 4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)phenyl ester

10

Example 972

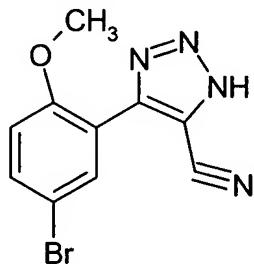
4-Chlorobenzoic acid 4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)phenyl ester

Example 973

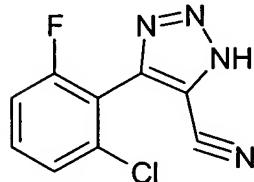
4-(3-Phenoxyphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile

5

Example 974

4-(5-Bromo-2-methoxyphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile

10 Example 975

4-(2-Chloro-6-fluorophenyl)-1*H*-[1,2,3]triazole-5-carbonitrile

The following cyanotriazoles are also compounds of the invention:

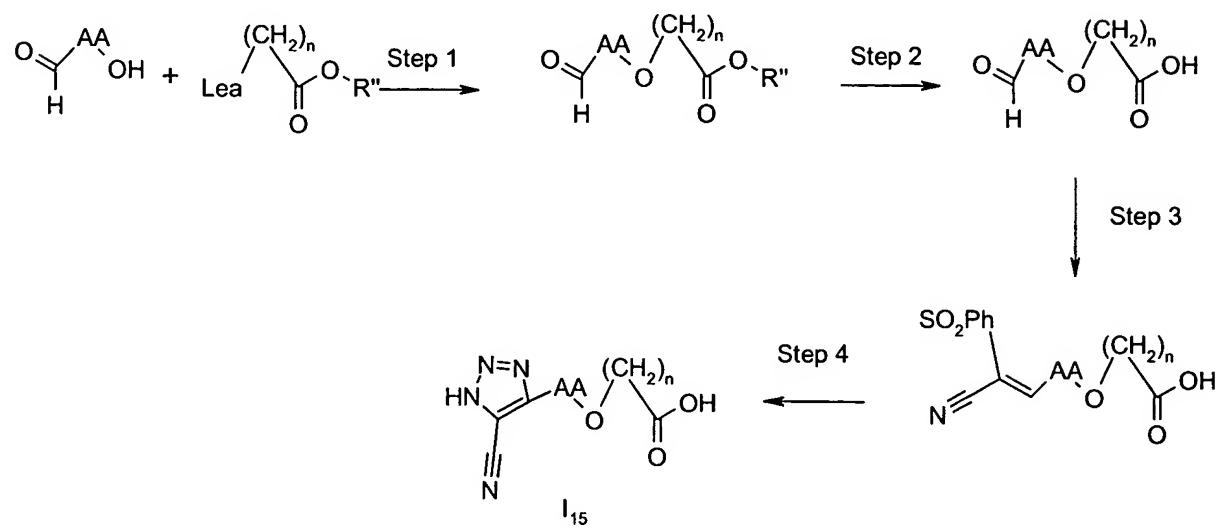
15

4-(2-Chloro-6-fluorophenyl)-1*H*-[1,2,3]triazole-5-carbonitrile.Terephthalic acid mono[4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)phenyl] ester.*N*-[4-(5-cyano-1*H*-[1,2,3]triazol-4-yl)-phenyl]terephthalamic acid4-(4-Octyloxyphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile20 4-(4-Styrylphenyl)-1*H*-[1,2,3]triazole-5-carbonitrile.4-(4'-Trifluoromethylbiphenyl-4-yl)-1*H*-[1,2,3]triazole-5-carbonitrile.4-(4'-Chlorobiphenyl-4-yl)-1*H*-[1,2,3]triazole-5-carbonitrile.4-(4'-Methoxybiphenyl-4-yl)-1*H*-[1,2,3]triazole-5-carbonitrile.4-(1-Naphthyl)-1*H*-[1,2,3]triazole-5-carbonitrile.

- 4-(9-Anthranyl)-1*H*-[1,2,3]triazole-5-carbonitrile.
 4-(4-Methoxy-1-naphthyl)-1*H*-[1,2,3]triazole-5-carbonitrile.
 4-(4-Aminophenyl)-1*H*-[1,2,3]triazole-5-carbonitrile.
 4-(2-Naphthyl)-1*H*-[1,2,3]triazole-5-carbonitrile.

5

General procedure (P) for preparation of compounds of general formula I₁₅:



- 10 wherein
 n is 1 or 3-20,
 AA is as defined above,
 R'' is a standard carboxylic acid protecting group, such as C₁-C₆-alkyl or benzyl and Lea is a leaving group, such as chloro, bromo, iodo, methanesulfonyloxy, toluenesulfonyloxy or the
 15 like.

This procedure is very similar to general procedure (D), steps 1 and 2 are identical.

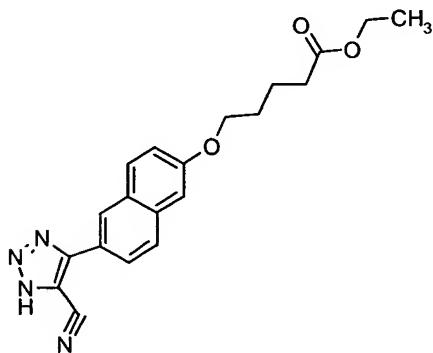
- 20 Steps 3 and 4 are described in the literature (eg Beck & Günther, *Chem. Ber.*, **106**, 2758-66 (1973))

Step 3 is a Knoevenagel condensation of the aldehyde obtained in step 2 with phenylsulfonylacetonitrile and step 4 is a reaction of the vinylsulfonate compound obtained in step 3 with sodium azide. This reaction is usually performed in DMF at 90 – 110 °C.

This General procedure (P) is further illustrated in the following two examples

Example 976 (General procedure (P))

- 5 5-[6-(5-Cyano-1H-[1,2,3]triazol-4-yl)-naphthalen-2-yloxy]-pentanoic acid ethyl ester



6-Hydroxynaphthalene-2-carbaldehyde (Syncrom BV. NL, 15.5 g, 90 mmol) and K₂CO₃ (62.2 g, 450 mmol) were mixed in DMF (300mL) and stirred at room temperature for 1hour. Ethyl 5-bromoalate (21.65 g, 103.5 mmol) was added and the mixture was stirred at room

- 10 temperature for 16 hours. Activated carbon was added and the mixture was filtered. The filtrate was evaporated to dryness *in vacuo* to afford 28.4 g of crude 5-(6-formylnaphthalen-2-yloxy)pentanoic acid ethyl ester, which was used without further purification.

HPLC-MS (Method C): m/z = 301 (M+1); Rt. = 4.39 min.

15

5-(6-Formylnaphthalen-2-yloxy)pentanoic acid ethyl ester (28.4 g, 94.5 mmol), phenylsulfonylacetonitrile (20.6 g, 113.5 mmol), and piperidine (0.94 mL) were dissolved in DMF (200 mL) and the mixture was heated at 50 °C for 16 hours. The resulting mixture was evaporated to dryness *in vacuo* and the residue was dried for 16 hours at 40 °C *in vacuo*.
 20 The solid was recrystallised from 2-propanol (800 mL) and dried again as described above. This afforded 35 g (80%) of 5-[6-(2-benzenesulfonyl-2-cyanovinyl)naphthalen-2-yloxy]pentanoic acid ethyl ester.

HPLC-MS (Method C): m/z = 486 (M+23); Rt. = 5.09 min.

25

5-[6-(2-Benzenesulfonyl-2-cyanovinyl)naphthalen-2-yloxy]pentanoic acid ethyl ester (35 g, 74.6 mmol) and sodium azide (4.9 g, 75.6 mmol) were dissolved in DMF (100 mL) and stirred

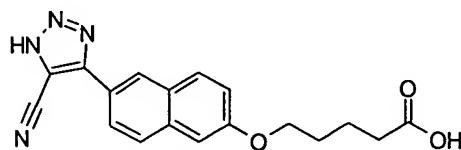
for 16 hours at 50 °C. The mixture was evaporated to dryness *in vacuo*, redissolved in THF / ethanol and a small amount of precipitate was filtered off. The resulting filtrate was poured into water (2.5 L). Filtration afforded after drying 24.5 g (88%) of 5-[6-(5-cyano-1*H*-[1,2,3]triazol-4-yl)naphthalen-2-yloxy]pentanoic acid ethyl ester (24.5 g, 88%).

5

HPLC-MS (Method C): m/z = 365 (M+1); Rt. = 4.36 min.

Example 977 (General procedure (B))

5-[6-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)-naphthalen-2-yloxy]-pentanoic acid



10

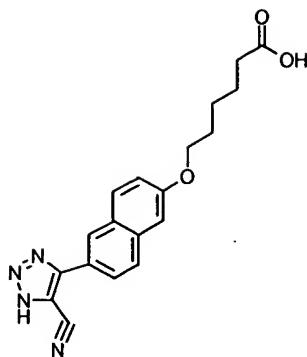
5-[6-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)naphthalen-2-yloxy]pentanoic acid ethyl ester (24.5 g, 67.4 mmol) was dissolved in THF (150 mL) and mixed with sodium hydroxide (8.1 g, 202 mmol) dissolved in water (50 mL). The mixture was stirred for 2 days and the volatiles were evaporated *in vacuo*. The resulting aqueous solution was poured into a mixture of water (1 L) and hydrochloric acid (1N, 250 mL). The solid was isolated by filtration, dissolved in sodium hydroxide (1N, 200 mL), and the solution was washed with DCM and then ethyl acetate, the aqueous layer was acidified with hydrochloric acid (12N). The precipitate was isolated by filtration, dissolved in THF / diethyl ether, the solution was treated with MgSO₄ and activated carbon, filtrated and evaporated *in vacuo* to almost dryness followed by precipitation by addition of pentane (1L). This afforded after drying *in vacuo* 17.2 g (76%) of the title compound.

HPLC-MS (Method C): m/z = 337 (M+1); Rt. = 3.49 min.

25 Example 978 (General procedure (P))

6-[6-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)naphthalen-2-yloxy]hexanoic acid

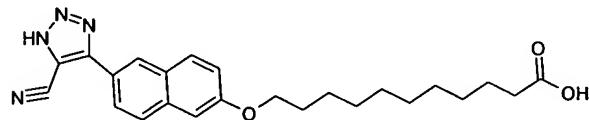
360



HPLC-MS (Method C): m/z = 351 (M+1); Rt = 3.68 min.

Example 979 (General procedure (P))

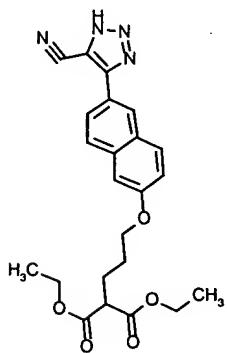
- 5 11-[6-(5-Cyano-1H-[1,2,3]triazol-4-yl)-naphthalen-2-yloxy]-undecanoic acid



HPLC-MS (Method C): m/z = 443 (M+23); Rt = 4.92 min.

Example 980 (General procedure (P))

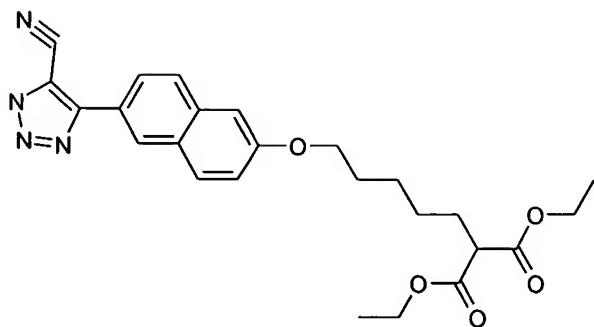
- 10 2-{3-[6-(5-Cyano-1H-[1,2,3]triazol-4-yl)-naphthalen-2-yloxy]-propyl}-malonic acid diethyl ester



HPLC-MS (Method C): m/z = 465 (M+1); Rt. = 4.95 min.

Example 981 (General procedure (P))

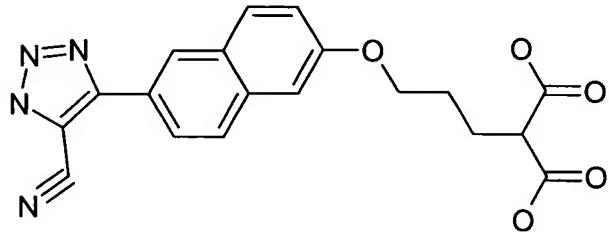
- 15 2-{5-[6-(5-Cyano-1H-[1,2,3]triazol-4-yl)-naphthalen-2-yloxy]-pentyl}-malonic acid diethyl ester



HPLC-MS (Method C): m/z = 465 (M+1); Rt. = 4.95 min.

Example 982 (General procedure (P))

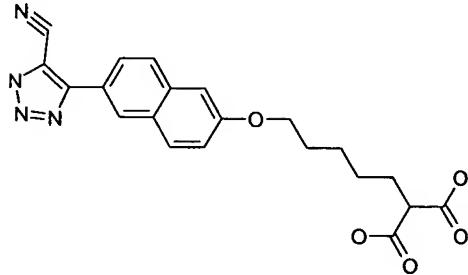
- 5 2-{3-[6-(5-Cyano-1H-[1,2,3]triazol-4-yl)-naphthalen-2-yloxy]-propyl}-malonic acid



HPLC-MS (Method C): m/z = 381 (M+1); Rt. = 3.12 min.

Example 983 (General procedure (P))

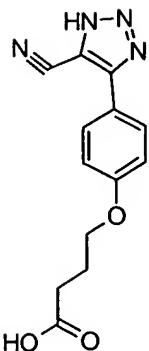
- 10 2-{5-[6-(5-Cyano-1H-[1,2,3]triazol-4-yl)-naphthalen-2-yloxy]-pentyl}-malonic acid



HPLC-MS (Method C): m/z 0 409 (M+1); Rt. = 3.51 min.

Example 984 (General procedure (P))

- 15 4-[4-(5-Cyano-1H-[1,2,3]triazol-4-yl)-phenoxy]butyric acid

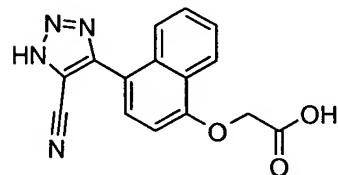
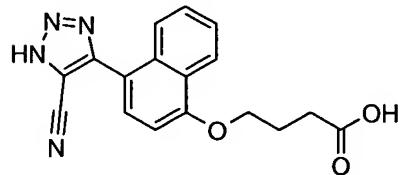


HPLC-MS (Method C): m/z = 273 (M+1); Rt = 2.44 min.

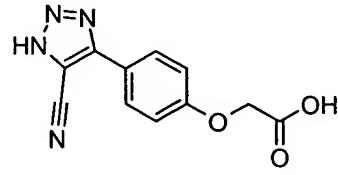
The following compounds may be prepared according to this general procedure (P):

5

4-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)butyric acid:



2-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)acetic acid:



10

4-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)butyric acid ethyl ester

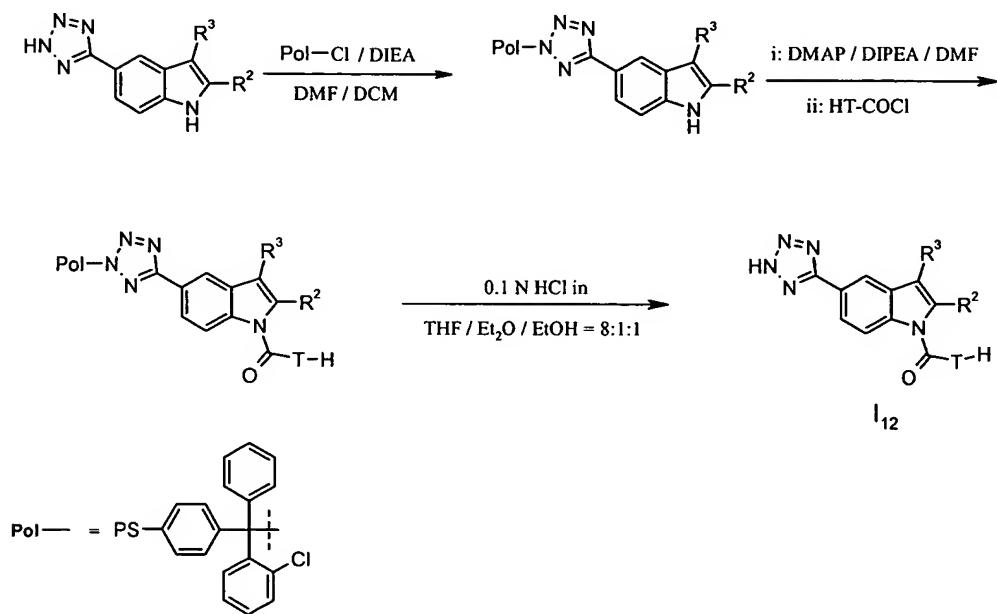
5-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)pentanoic acid

8-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)octanoic acid

10-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)decanoic acid

15

12-(4-(5-Cyano-1*H*-[1,2,3]triazol-4-yl)phenoxy)dodecanoic acid

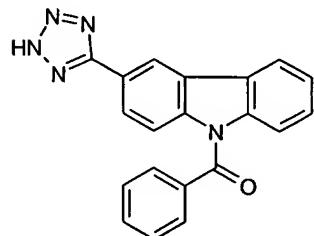
General procedure (R) for preparation of compounds of general formula I₁₂:

- 5 wherein T is as defined above and R² and R³ are hydrogen, aryl or lower alkyl, both optionally substituted.

The general procedure (R) is further illustrated by the following example:

10 Example 985 (General procedure (R))

Phenyl-[3-(2H-tetrazol-5-yl)-carbazol-9-yl]-methanone



- 15 2-Chlorotriptylchloride resin (100 mg, 0.114 mmol active chloride) was swelled in dichloromethane (4 mL) for 30 minutes. The solvent was drained, and a solution of 3-(2H-tetrazol-5-yl)-9H-carbazole (80 mg, 0.34 mmol) in a mixture of N,N-dimethylformamide / dichloromethane / N,N-di(2-propyl)ethylamine (5:5:1) (3 mL) was added. The reaction mixture was shaken at room temperature for 20 hours. The solvent was removed by filtration, and the resin was washed thoroughly with N,N-dimethylformamide (2 x 4 mL) and

dichloromethane (6 x 4 mL). A solution of 4-(dimethylamino)pyridine (14 mg, 0.11 mmol) and N,N-di(2-propyl)ethylamine (0.23 mL, 171 mg, 1.32 mmol) in N,N-dimethylformamide (2 mL) was added followed by benzoyl chloride (0.13 mL, 157 mg, 1.12 mmol). The mixture was shaken for 48 hours at room temperature. The drained resin was washed consecutively with 5 dichloromethane (2 x 4 mL), methanol (2 x 4 mL) and tetrahydrofuran (4 mL). The resin was treated for 2 hours at room temperature with a solution of dry hydrogen chloride in tetrahydrofuran / ethyl ether / ethanol = 8:1:1 (0.1 M, 3 mL). The reaction mixture was drained and concentrated. The crude product was stripped with dichloromethane (1.5 mL) three times to yield the title compound.

10

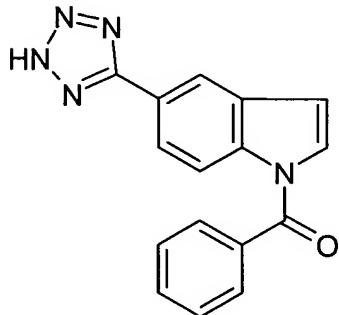
HPLC-MS (Method C): m/z: 340 (M+1); Rt = 3.68 min.

¹H-NMR (DMSO-d₆): δ 8.91 (1H, s), 8.34 (1H, d), 8.05 (1H, d), 7.78 (3H, m), 7.63 (3H, m), 7.46 (2H, m), 7.33 (1H, dd).

15 The compounds in the following examples were prepared in a similar fashion.

Example 986 (General procedure (R))

Phenyl-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone

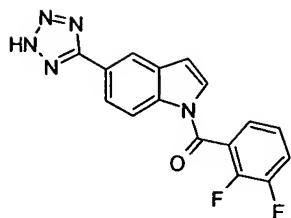


20 HPLC-MS (Method C): m/z: 290 (M+1); Rt = 3.04 min.

¹H-NMR (DMSO-d₆): δ 8.46 (1H, d), 8.42 (1H, d), 8.08 (1H, dd), 7.82 (2H, d), 7.74 (1H, t), 7.64 (2H, t), 7.55 (1H, d), 6.93 (1H, d).

Example 987 (General procedure (R))

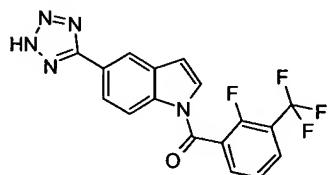
25 (2,3-Difluorophenyl)-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone



HPLC-MS (Method B): m/z = 326 (M+1); Rt = 3.85 min.

Example 988 (General procedure (R))

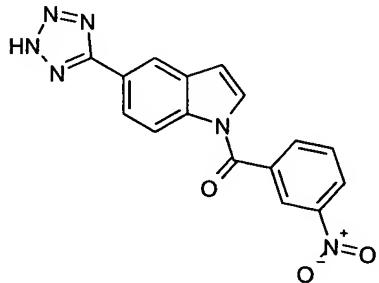
- 5 (2-Fluoro-3-trifluoromethylphenyl)-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone



HPLC-MS (Method B): m/z = 376 (M+1); Rt = 4.32 min.

Example 989 (General procedure (R))

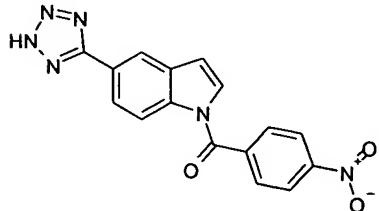
- 10 (3-Nitrophenyl)-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone



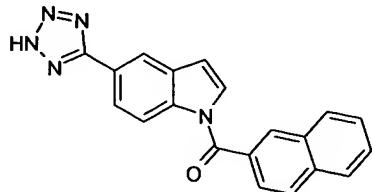
HPLC-MS (Method B): m/z = 335 (M+1); Rt = 3.72 min.

Example 990 (General procedure (R))

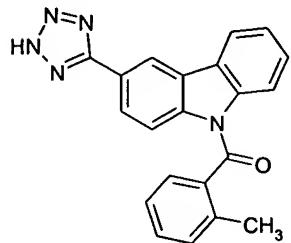
- 15 (4-Nitrophenyl)-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone



HPLC-MS (Method B): m/z = 335 (M+1); Rt = 3.71 min.

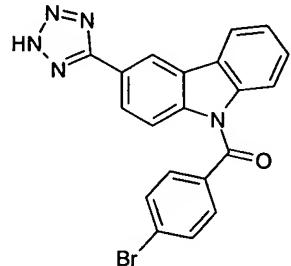
Example 991 (General procedure (R))**Naphthalen-2-yl-[5-(2H-tetrazol-5-yl)-indol-1-yl]-methanone**

- 5 HPLC-MS (Method C): m/z = 340 (M+1); Rt = 4.25 min.

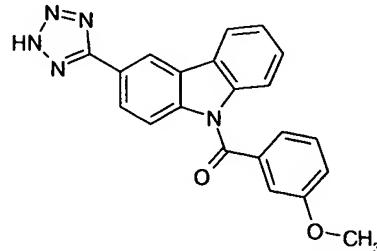
Example 992 (General procedure (R))

HPLC-MS (Method C): m/z: 354 (M+1); Rt = 3.91 min.

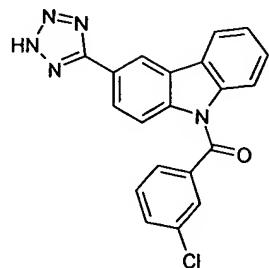
10

Example 993 (General procedure (R))

HPLC-MS (Method C): m/z: 418 (M+1); Rt = 4.39 min.

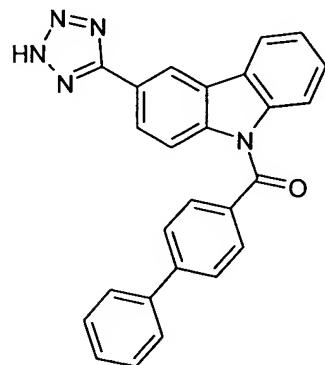
15 **Example 994 (General procedure (R))**

HPLC-MS (Method C): m/z: 370 (M+1); Rt = 4.01 min.

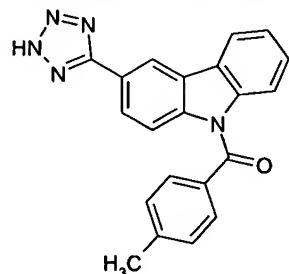
Example 995 (General procedure (R))

HPLC-MS (Method C): m/z: 374 (M+1); Rt = 4.28 min.

5

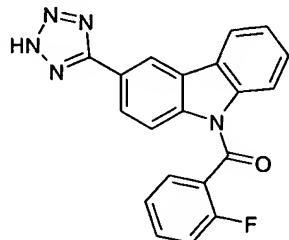
Example 996 (General procedure (R))

HPLC-MS (Method C): m/z: 416 (M+1); Rt = 4.55 min.

10 **Example 997 (General procedure (R))**

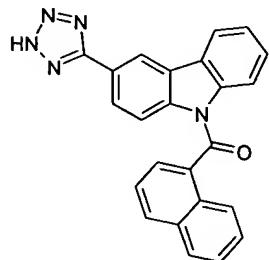
HPLC-MS (Method C): m/z: 354 (M+1); Rt = 4.22 min.

Example 998 (General procedure (R))



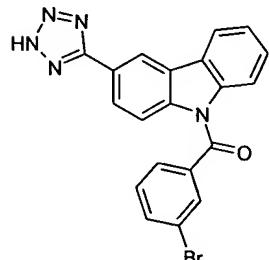
HPLC-MS (Method C): m/z: 358 (M+1); Rt = 3.91 min.

5 Example 999 (General procedure (R))



HPLC-MS (Method C): m/z: 390 (M+1); Rt = 4.38 min.

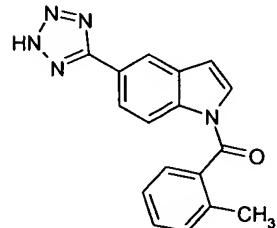
Example 1000 (General procedure (R))



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HPLC-MS (Method C): m/z: 418 (M+1); Rt = 4.36 min.

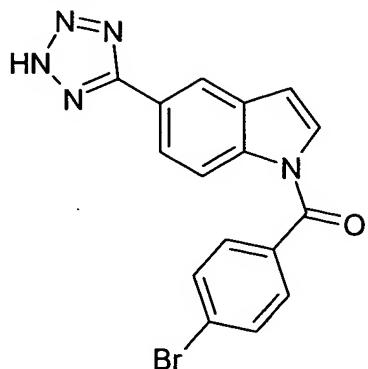
Example 1001 (General procedure (R))



15

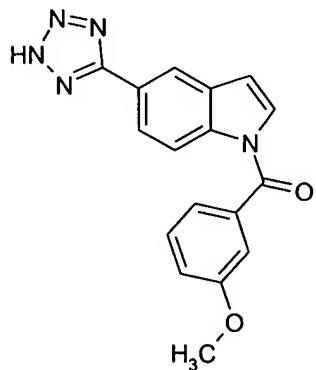
HPLC-MS (Method C): m/z: 304 (M+1); Rt = 3.32 min.

Example 1002 (General procedure (R))



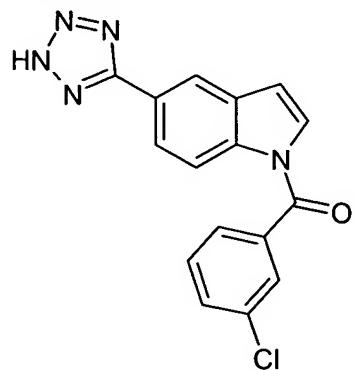
HPLC-MS (Method C): m/z: 368 (M+1); Rt = 3.84 min.

5 Example 1003 (General procedure (R))



HPLC-MS (Method C): m/z: 320 (M+1); Rt = 3.44 min.

Example 1004 (General procedure (R))

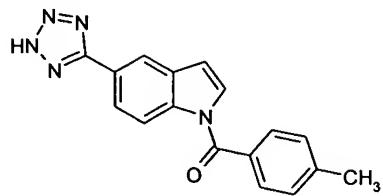


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HPLC-MS (Method C): m/z: 324 (M+1); Rt = 3.73 min.

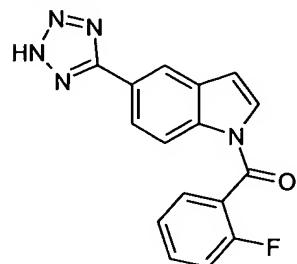
370

Example 1005 (General procedure (R))



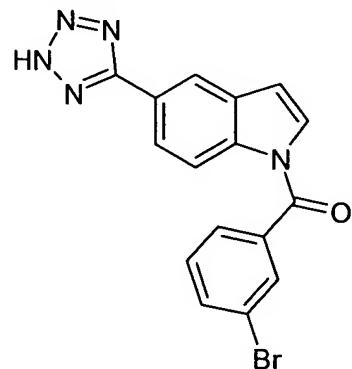
HPLC-MS (Method C): m/z: 304 (M+1); Rt = 3.64 min.

5 Example 1006 (General procedure (R))



HPLC-MS (Method A): m/z: 308 (M+1); Rt = 3.61 min.

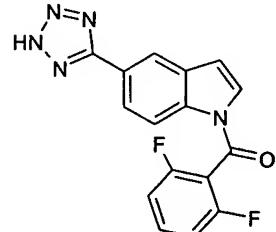
Example 1007 (General procedure (R))



10

HPLC-MS (Method C): m/z: 368 (M+1); Rt = 3.77 min.

Example 1008 (General procedure (R))

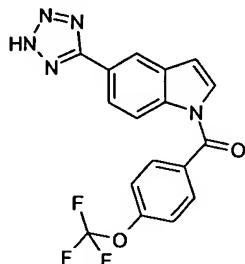


15

HPLC-MS (Method A): (sciex) m/z: 326 (M+1); Rt = 3.73 min.

HPLC-MS (Method C): m/z: 326 (M+1); Rt = 3.37 min.

Example 1009 (General procedure (R))



5 HPLC-MS (Method C): m/z: 374 (M+1); Rt = 4.03 min.

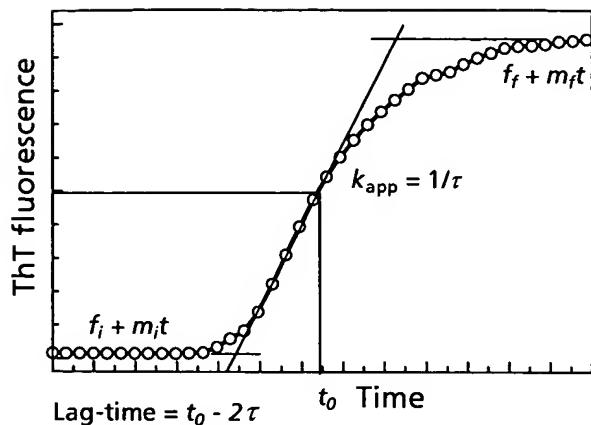
Example 1010 Characterization of ligand effects on physical stability of formulations by the Thioflavine T fluorescence assay.

- 10 Low physical stability of insulin formulations may lead to amyloid fibril formation, which is observed as well-ordered, thread-like macromolecular structures in the sample eventually resulting in gel formation. This has traditionally been measured by visual inspection of the sample. However, the application of a small molecule indicator probe is much more preferable. Thioflavin T is such a probe and has a distinct fluorescence signature when
- 15 binding to fibrils (or rather β -sheet rich proteins) [Naiki et al. (1989) Anal. Biochem. **177**, 244-249; LeVine (1999) Methods. Enzymol. **309**, 274-284]. Its application to insulin fibrillation has recently been validated [Nielsen et al. (2001) Biochemistry **40**, 6036-6046].
The time course for fibril formation can be described by a sigmoidal curve with the following expression:

20

$$F = f_i + m_f t + \frac{f_f + m_f t}{1 + e^{-[(t-t_0)/\tau]}} \quad \text{Eq.(2)}$$

- Here, F is the ThT fluorescence at the time t . The constant t_0 is the time needed to reach 50% of maximum fluorescence. The minimum and maximum fluorescence is denoted f_i and f_f , respectively, and the expressions $m_f t$ and $m_f t$ describe the linear development of the bottom and top base lines. The two important parameters describing fibril formation are the lag-time calculated by $t_0 - 2\tau$ and the apparent rate constant $k_{app} = 1/\tau$.



- Formation of a partially folded intermediate of the protein is suggested as a general initiating mechanism for fibrillation. Few of those intermediates nucleate to form a template onto which further intermediates may assemble and the fibrillation is initiated. The lag-time corresponds to the interval in which the critical mass of nucleus is built up and the apparent rate constant is the rate with which the fibril itself is formed.
- In accordance with this mechanism, insulin needs to dissociate to its monomeric form before a partially folded intermediate may be formed. Keeping insulin on a multimeric form may therefore result in increased physical stability. Ligands binding to the insulin hexamer zinc site should stabilize the hexameric form and draw the equilibrium even further away from the monomeric form. Hence, an increased physical stability could be achieved.

Sample preparation

- Insulin formulations were prepared freshly before each assay from appropriate stock solutions. Typical final concentrations were 0.6 mM human insulin or insulin aspart analogue, 0.2 mM ZnAc, 30 mM phenol, 10 mM Tris pH 8. ThT was added from a 1 mM stock solution in water to a final concentration of 1 μ M. The formulations were typically prepared in double concentration and mixed with an equal volume of test compound in appropriate concentration in 4% DMSO, 10 mM Tris pH 8.
- Alternatively, insulin aspart formulations (100 U/ml) from the production line were used directly. ThT was added to 1 μ M and DMSO containing test compound in appropriate concentration to 2%.
- Sample aliquots of 200 μ l were placed in a 96 well microtiter plate (Packard OptiPlateTM-96, white polystyrene). Usually, eight replica of each sample (corresponding to one test

compound concentration) was placed in one column of wells. The plate was sealed with Scotch Pad (Qiagen).

Control experiments for possible test compound quenching of the ThT emission were carried out using human insulin without Zn²⁺ and phenol i.e. in a non-hexameric configuration.

- 5 Hence, the fibrillation process as well as the ThT emission should be unaffected by the presence of test compound, unless it quenched the ThT signal.

Incubation and fluorescence measurement

Temperature incubation, shaking and measurement of the ThT fluorescence were done in a

- 10 Fluoroskan Ascent FL fluorescence platereader (Thermo Labsystems). Temperature setting is possible up till 45 °C, but usually set at 30 °C. Heating was initiated at first measurement. The orbital shaking is selectable up till 1200 rpm, but adjusted to 960 rpm in all the presented data with an amplitude of 1 mm.

Fluorescence measurement was done using excitation through a 444 nm filter and

- 15 measurement of emission through a 485 nm filter. Each run was initiated by a measurement and intervals between measurements were usually 20 min. The plate was shaken and heated as adjusted between each measurement. The assay time was regulated by the number of measurements and the interval in between. Usually the plate was measured 46 times with 20 min between, i.e. over 15 hours.

20

Data handling

The measurement points were saved in Microsoft Excel format for further processing and curve drawing and fitting was performed using GraphPad Prism. The background emission from ThT in the absence of fibrils was negligible. Some test compounds had background

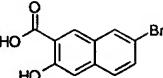
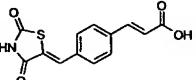
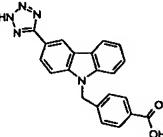
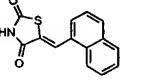
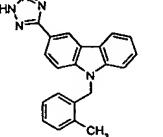
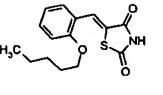
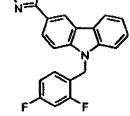
- 25 fluorescence under the applied experimental conditions. This was eliminated by subtracting the mean value of the first measurement from the data set for this test compound. The data points are shown with standard deviation.

The data set may be fitted to Eq. (2). However, since the stabilizing effect of the test compounds/ligands were so significant that a full sigmoid curve was not obtained during the
30 usual assay time, curve fitting to such a data set would be imprecise and hence meaningless.

Only data obtained in the same experiment (i.e. samples on the same plate) are presented in the same graph.

- 35 Examples & Results

The various ligands are shown below with structure and affinity towards the zinc site as measured by the TZD-assay described in "Analytical Methods".

Reference	Example	Compound	$K_d(\text{app})$ (nM)
A	533		383
C	462		58
D	738		171
E	68		23
F	756		3
G	1		3879
H	76		82
I	759		23

The ThT assays of various combinations of insulin formulations and ligands are shown in Fig.

5 1 – 8.

Addition of ligands improves the physical stability of insulin formulations. This holds for human insulin formulations (see Fig 1) as well as insulin aspart formulations (rest of data set).

The improved stability can be obtained by using various compound classes as zinc site anchor, e.g. benzothiazoles (G, Fig 1), naphthosalicylic acids (A, Fig 2), thiazolidine-diones (E, Figs 4, 7; C, Fig 2; H, Figs 6, 8) and tetrazoles (D, Fig 3; F, Fig 8; I, Fig 5).

- 5 Increased affinity of the ligand results in higher stability of the formulation. Compare the effect of the weakest binding ligand in 2 mM (G, Fig. 1) with the effect on an insulin aspart formulation of 0,5 mM E (Fig. 4). Also compare the effects of similar concentrations of A and C (Fig 2); and of D (fig. 3) and E (Fig 4) on insulin aspart formulations.
 - 10 Increasing the concentration of ligand tends to improve the stabilization (see Figs. 1, 3, 4, 5, 6). In some instants, more pronounced effects are seen with the ligand in slight molar excess to the zinc sites, see Figs. 4, 6, whereas it seems to plateau around the stoichiometric concentration in other instances (Figs. 3, 5).
 - 15 Of the presented ligands, A, C, D, E, F were tested in a disappearance assay for the effect on release of insulin aspart from a subcutaneous inject site. Surprisingly, the ligands had no effect on the insulin aspart disappearance. In a very limited way, this can be mimicked in the ThT assay by increasing the assay temperature to 37 °C (see Figs. 7, 8). The stabilizing effect is somewhat attenuated, e.g. compare E at 30 °C (Fig 4) and 37 °C (Fig 7), and H (Fig 20 6 and 8). The ligand with highest affinity (F) has the most stabilizing effect at 37 °C (Fig. 8).

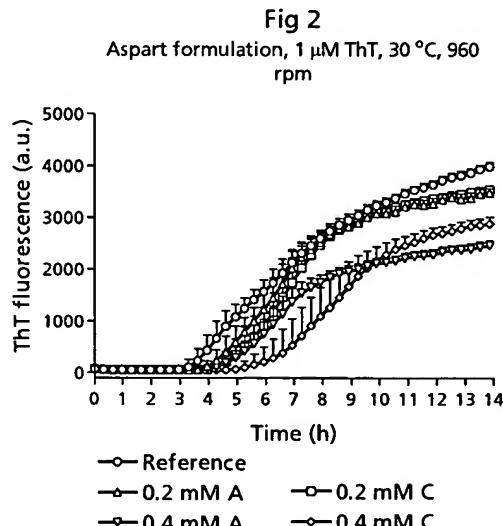
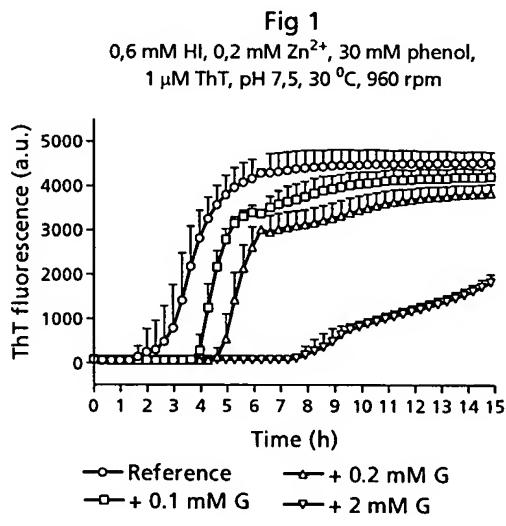


Fig 3
Aspart Formulation, 1 μ M ThT, 30 °C, 960 rpm.

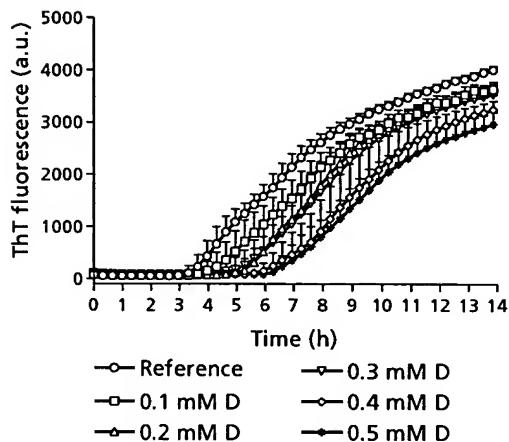


Fig 5
Aspart formulation, 1 μ M ThT, pH 8, 30 °C,
960 rpm.

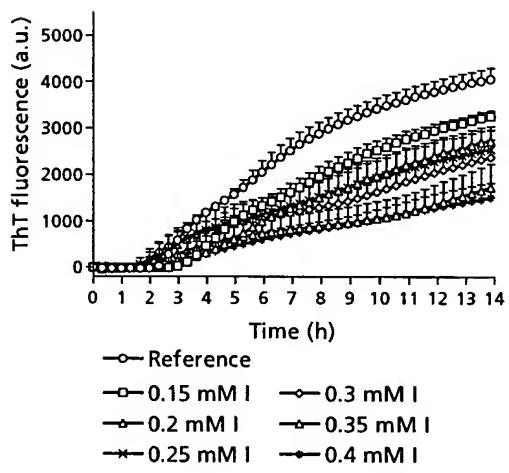


Fig 4
Aspart formulation, 1 μ M ThT, 30 °C, 960 rpm.

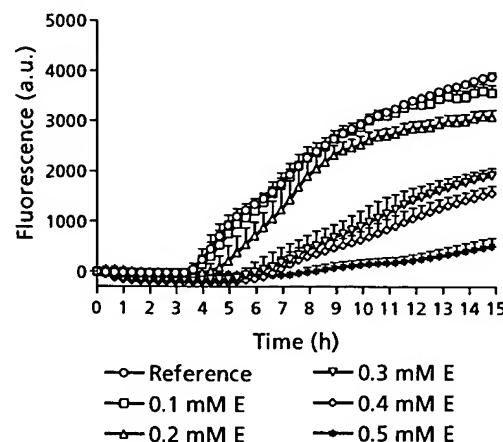
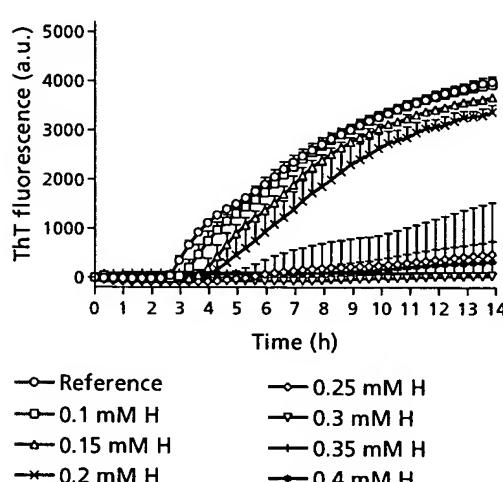


Fig 6
Aspart formulation, 1 μ M ThT, pH 8, 30 °C,
960 rpm.



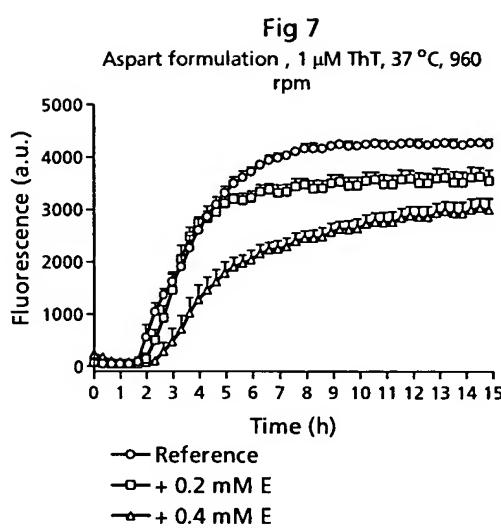
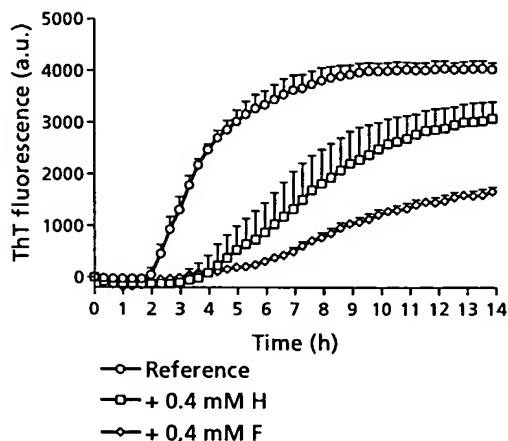


Fig 8
Aspart formulation, 1 μ M ThT, 37 °C, 960 rpm.



Example 1011 Retention of fast absorption characteristics of formulations stabilized by addition of His^{B10} Zn²⁺-site ligands.

5

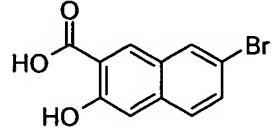
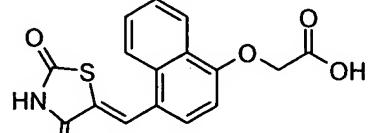
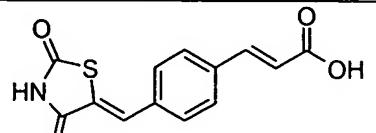
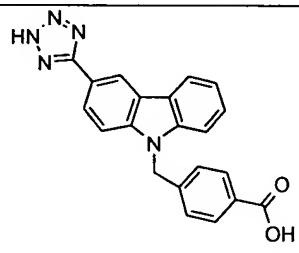
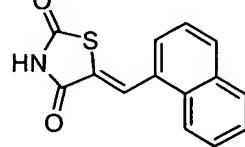
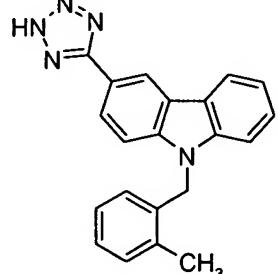
Formulations of the present invention were characterized by the disappearance rate from the subcutaneous depot following injection in pigs. Formulations of B28 Asp human insulin containing A14Tyr(¹²⁵I) B28 Asp human insulin were followed with an external γ -counter (Ribet et al., The pig as a model for subcutaneous absorption in man. In: Serrano-Ritos &

- 10 Lefebre (Eds.): Diabetes (1985) proceedings of the 12th congress of the international diabetes federation, Madrid, Spain, 1985 (Excerpta Medica, Amsterdam (1986) 891-896. Formulations of Insulin Aspart (0.6 mM, U100) containing 0.3 mM Zn²⁺, 30 mM phenol, 2 mM phosphate buffer, and 1.6% glycerol, pH 7.4, were compared with the corresponding formulations containing 0.3 mM of the ligands shown below: where T_{50%} is the time when 15 50% of the A14Tyr(¹²⁵I) B28 Asp insulin has disappeared from the site of injection and K_d is the affinity of the ligand as measured by the TZD-assay described in "Analytical methods" below. It is evident that the stabilizing ligands do not affect the fast absorption properties of the formulations

20

	Example #	Compound	T50%	K _d (app) (nM)
reference			1.3± 0.3	

378

A	533		1.0± 0.23	383
B	476		1.1± 0.37	68
C	462		0.9± 0.19	58
D	738		1.3± 0.36	171
E	68		1.2± 0.41	23
F	756		1.2± 0.27	3

379

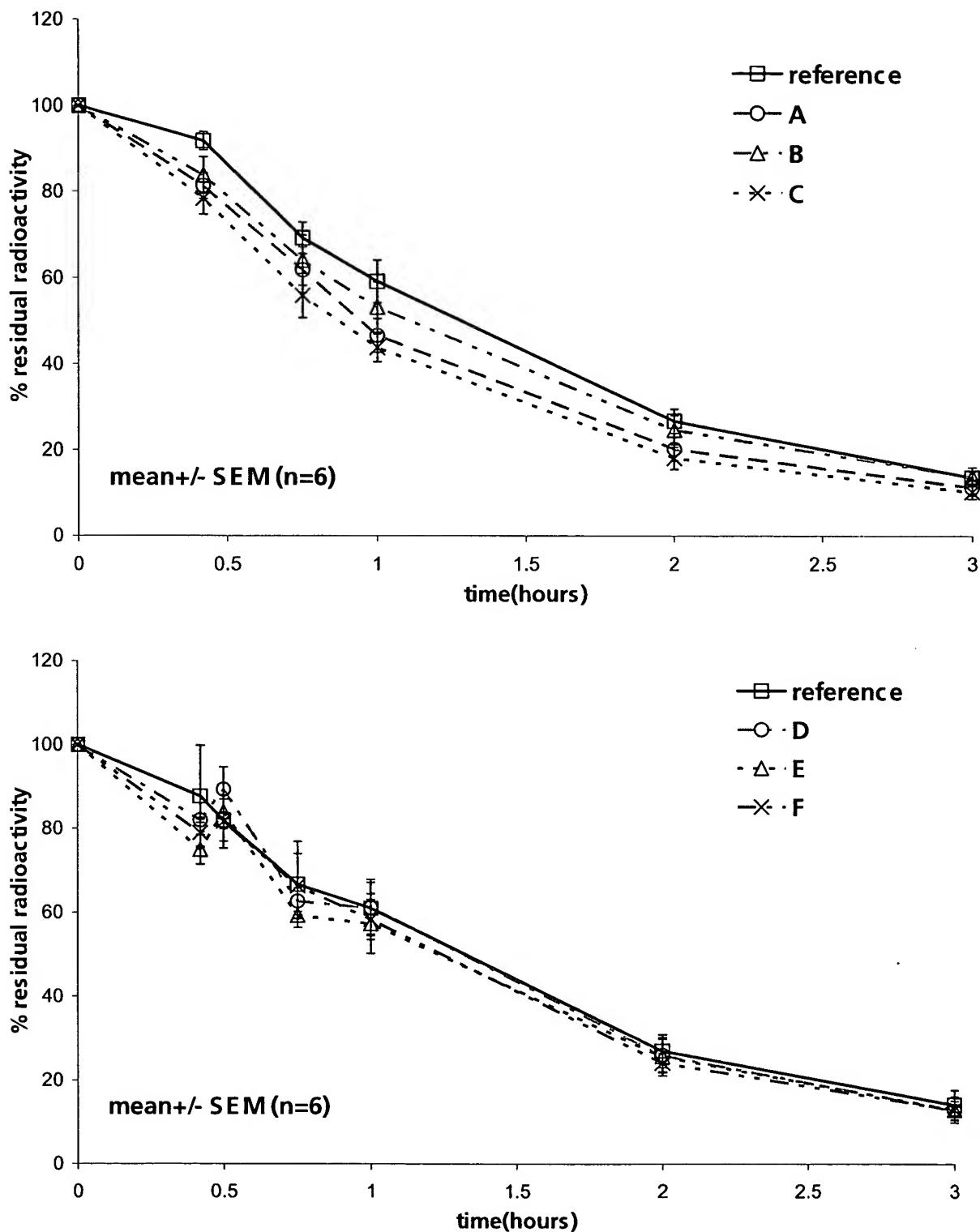
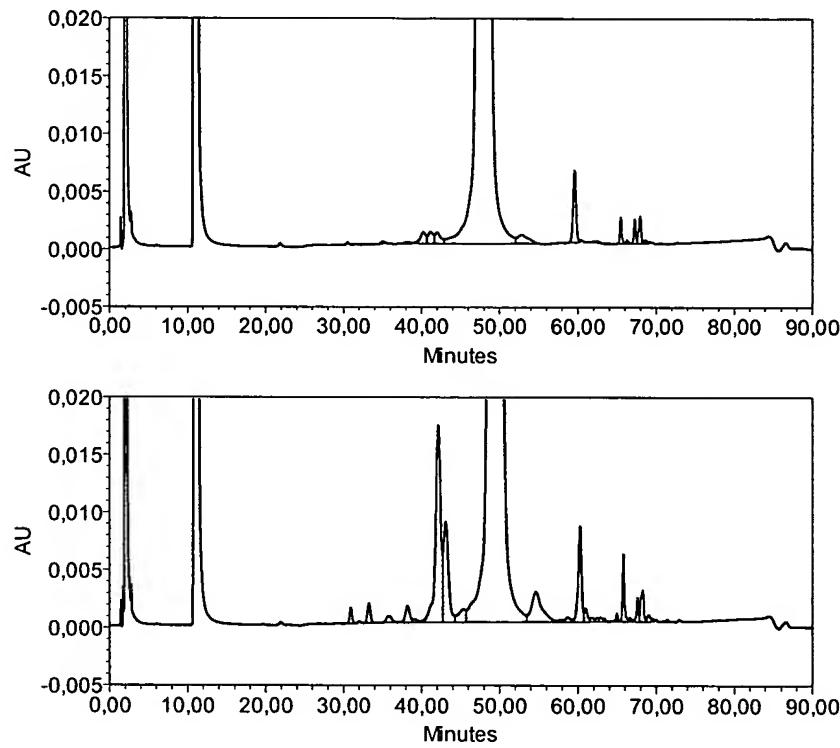


Figure 9

Example 1012**Reference experiment**

- 5 The chemical stability of insulin formulations of the invention was characterised by HPLC (RPC, reverse phase chromatography and SEC, size exclusion chromatography). As reference, insulin formulated without ligands of the invention but with 0.3 % DMSO was also investigated and shown below:



10

Figure 10

- Fig 10.** Reverse phase chromatography of formulated human insulin with 3 Zn²⁺ per hexamer, 30 mM phenol, 150 mM mannitol, 3 mM phosphoric acid, sodium hydroxide to pH 7.4 and 0.3 % DMSO corresponding to 3 ligands per hexamer at start (upper panel) and after 15 storage for 2 weeks at 37 °C (lower panel): Preservatives before 20 min., "hydrophilic

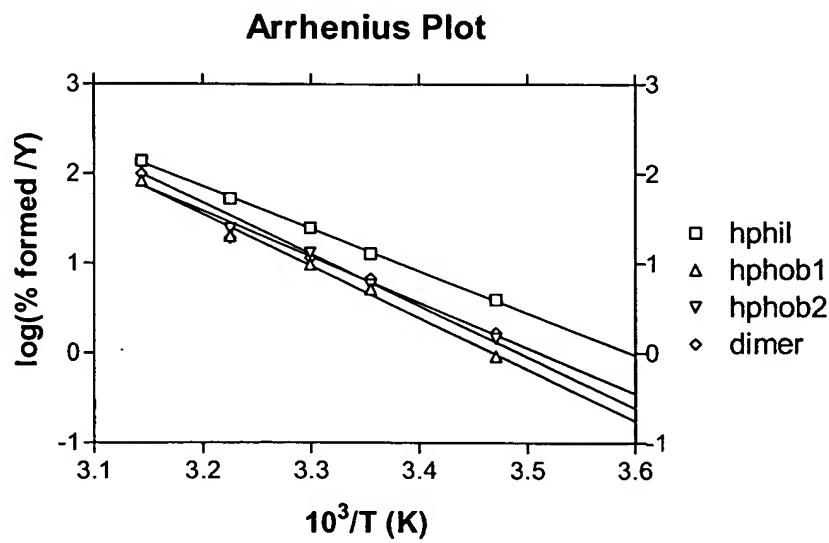
derivatives" (desamido-insulins) 20 min to main top insulin, "hydrophobic derivatives 1" main top to 64 min., and "hydrophobic derivatives 2" (insulin dimers) after 64 min.

Storage in HPLC 1 ml vials at 45 °C (5 d), 37 °C (2 w), 30 °C (6 w), 25 °C (10 w), 15 °C (30 w) gave about the same increase of transformation products correlating to an increase in reactions constants of a factor 3-4 per 10 degree..

RPC (reverse phase chromatography) on Waters SymmetryShield RP₈ column, 150×4.6 mm and 3.5 μm, eluted by **A**: 0.2 M sodium sulfate + 0.04 M sodium phosphate pH 7.2 + 10 % acetonitrile and isocratically (i) or a gradient (g) of **B**: 70 % acetonitrile [minutes/%B(i/g): 0/19, 21/24(i)(sudden change), 51/24(i), 81/39(g), 81.1/0(i), 82.3/19(i)] at flow of 0.9 mL/min and 30 °C.

SEC (size exclusion chromatography) on Waters insulin HMWP column, 300×7.8 mm, eluted by 15:20:65 of acetic acid: acetonitrile: arginine 1 g/L at flow of 1 mL/min and ambient temperature.

% formed/year	RPC			SEC
	hphil	hphob1	hphob2	dimer
45°C	153.3	47.5	23.4	21.9
37°C	57.2	15.6	5.20	6.24
30°C	24.5	4.16	1.30	2.08
25°C	14.2	2.13	0.68	1.09
15°C	4.12	0.43	0.22	0.31
5°predicted	(1.001)	(0.066)	(0.027)	(0.052)

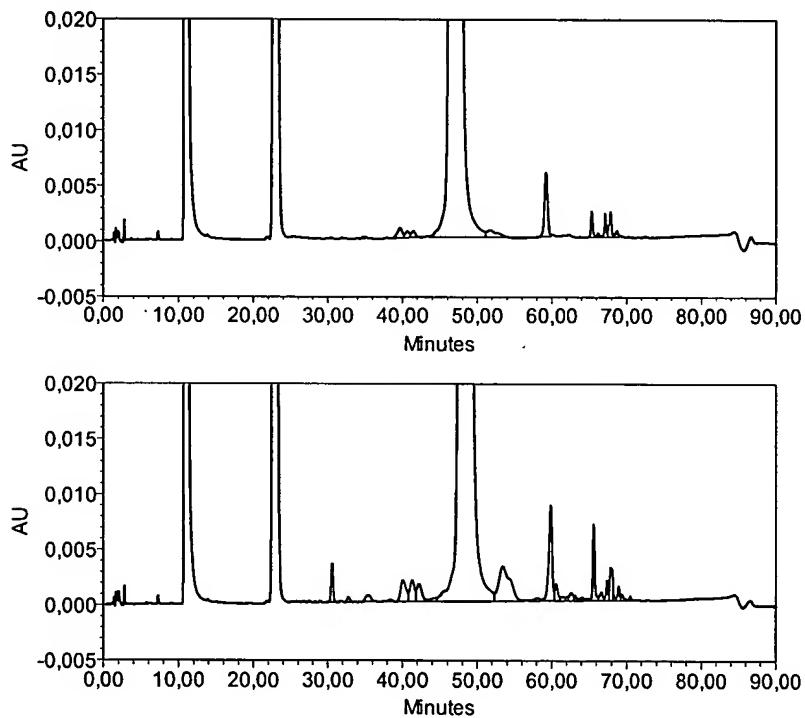


The chemical stability of insulin formulations of the invention was likewise characterised by HPLC (RPC, reverse phase chromatography and SEC, size exclusion chromatography). Compared to the reference the formulations of the invention were shown to be more chemically stable.

5

Example 1013

Chemical stability of insulin formulated with the compound of example 533 , 7-bromo-3-hydroxy-2-naphthoic acid:



10

Figure 11

Fig 11. Reverse phase chromatography of formulated human insulin as described for the reference example and added 3 ligands of Example 533 and 3 Zn²⁺ per hexamer at start (upper panel) and after storage for 2 weeks at 37 °C (lower panel): Preservatives before 20 min., "hydrophilic derivatives" (desamido-insulins) 20 min to main top insulin, "hydrophobic derivatives 1" main top to 64 min., and "hydrophobic derivatives 2" (insulin dimers) after 64 min.

Storage in HPLC 1 ml vials at 45 °C (5 d), 37 °C (2 w), 30 °C (6 w), 25 °C (10 w), 15 °C (30 w) will give about the same increase in transformation products correlating to an increase in reaction constants of a factor 3-4 per 10 degrees...

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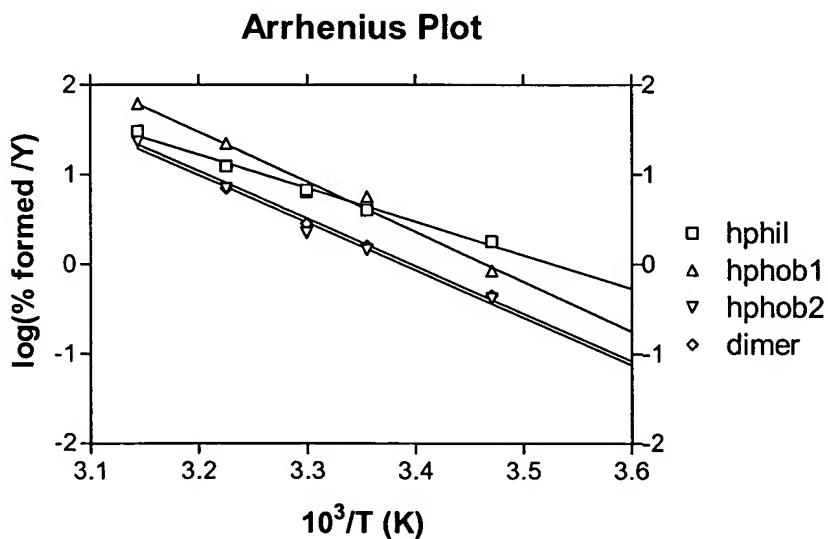
RPC (reverse phase chromatography) on Waters SymmetryShield RP₈ column, 150×4.6 mm and 3.5 µm, eluted by **A**: 0.2 M sodium sulfate + 0.04 M sodium phosphate pH 7.2 + 10 % acetonitrile and isocratically (i) or a gradient (g) of **B**: 70 % acetonitrile [minutes/%B(i/g): 0/19, 21/24(i)(sudden change), 51/24(i), 81/39(g), 81.1/0(i), 82.3/19(i)] at flow of 0.9 mL/min and 30 °C.

10

SEC (size exclusion chromatography) on Waters insulin HMWP column, 300×7.8 mm, eluted by 15:20:65 of acetic acid: acetonitrile:arginine 1 g/L at flow of 1 mL/min and ambient temperature.

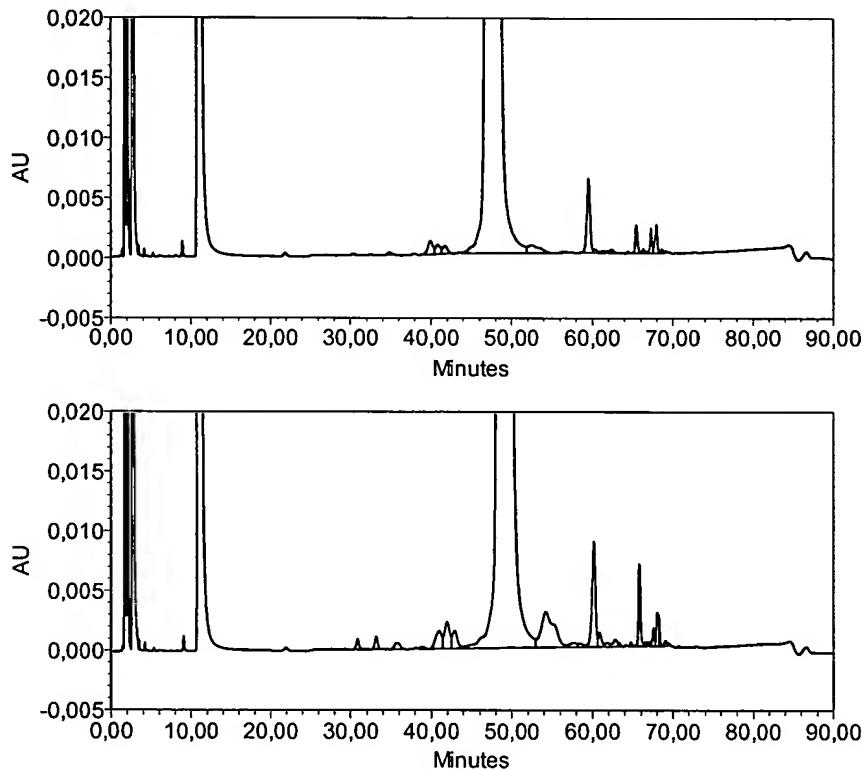
15

% formed/year	RPC			SEC
	hphil	hphob1	hphob2	dimer
45°C	30.7	62.1	23.4	26.3
37°C	12.5	22.4	7.02	7.02
30°C	6.76	6.42	2.25	2.86
25°C	4.06	5.67	1.46	1.61
15°C	1.80	0.85	0.42	0.45
5°predicted	(0.55)	(0.19)	(0.079)	(0.087)



Example 1014

Chemical stability of insulin formulated with the compound of Example 462, 3-[4-(2,4-dioxothiazolidin-5-ylidenemethyl)phenyl]acrylic acid:



5

Figure 12

Fig 12. Reverse phase chromatography of formulated human insulin as described for the reference example and added 3 ligands of example 462 and 3 Zn²⁺ per hexamer at start
10 (upper panel) and after storage for 2 weeks at 37 °C (lower panel): Preservatives before 20 min., "hydrophilic derivatives" (desamido-insulins) 20 min to main top insulin, "hydrophobic derivatives 1" main top to 64 min., and "hydrophobic derivatives 2" (insulin dimers) after 64 min.

Storage in HPLC 1 ml vials at 45 °C (5 d), 37 °C (2 w), 30 °C (6 w), 25 °C (10 w), 15 °C (30 w) will give about the same increase in transformation products correlating to an increase in reaction constants of a factor 3-4 per 10 degrees.

- 5 **RPC** (reverse phase chromatography) on Waters SymmetryShield RP₈ column, 150×4.6 mm and 3.5 µm, eluted by **A**: 0.2 M sodium sulfate + 0.04 M sodium phosphate pH 7.2 + 10 % acetonitrile and isocratically (i) or a gradient (g) of **B**: 70 % acetonitrile [minutes/%B(i/g): 0/19, 21/24(i)(sudden change), 51/24(i), 81/39(g), 81.1/0(i), 82.3/19(i)] at flow of 0.9 mL/min and 30 °C.

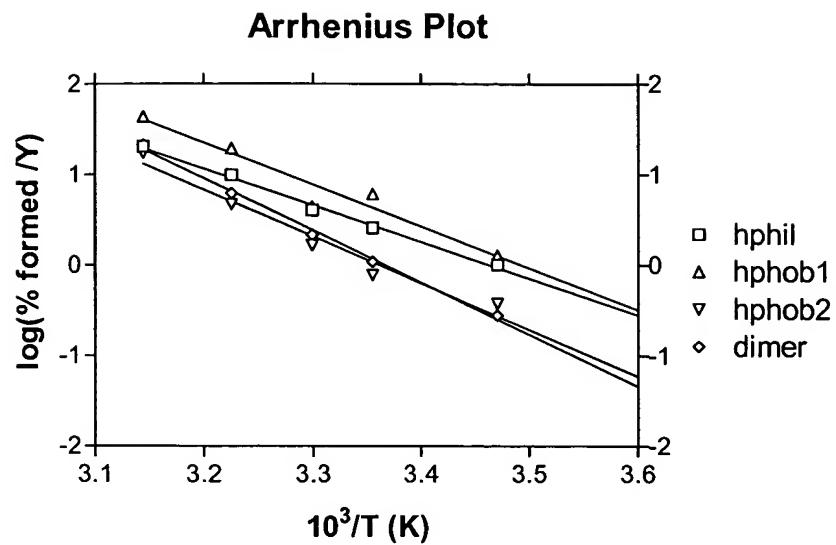
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SEC (size exclusion chromatography) on Waters insulin HMWP column, 300×7.8 mm, eluted by 15:20:65 of acetic acid: acetonitrile:arginine 1 g/L at flow of 1 mL/min and ambient temperature.

% formed/year	RPC			SEC
	hphil	hphob1	hphob2	Dimer
45°C	20.4	43.8	17.5	21.2
37°C	9.88	19.5	4.68	6.24
30°C	4.07	4.42	1.65	2.17
25°C	2.60	6.14	0.78	1.09
15°C	1.02	1.28	0.38	0.28
5°predicted	(0.293)	(0.336)	(0.062)	(0.048)

15

386

**Example 1015**

Chemical stability of insulin formulated with the compound of example 461 , [3-(2,4-Dioxothiazolidin-5-ylidenemethyl)phenoxy]acetic acid:

5

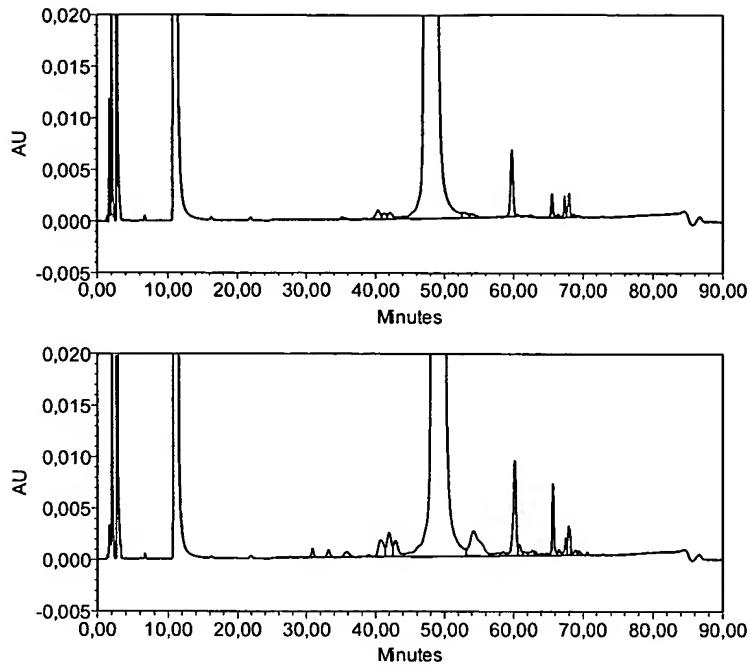


Fig 13. Reverse phase chromatography of formulated human insulin added 3 ligands (#) and 3 Zn per hexamer at start and storage of 2 w 37 °C: Preservatives before 20 min., "hydrophilic derivatives" (desamido-insulins) 20 min to main top insulin, "hydrophobic derivatives 1" main top to 64 min., and "hydrophobic derivatives 2" (insulin dimers) after 64 min.

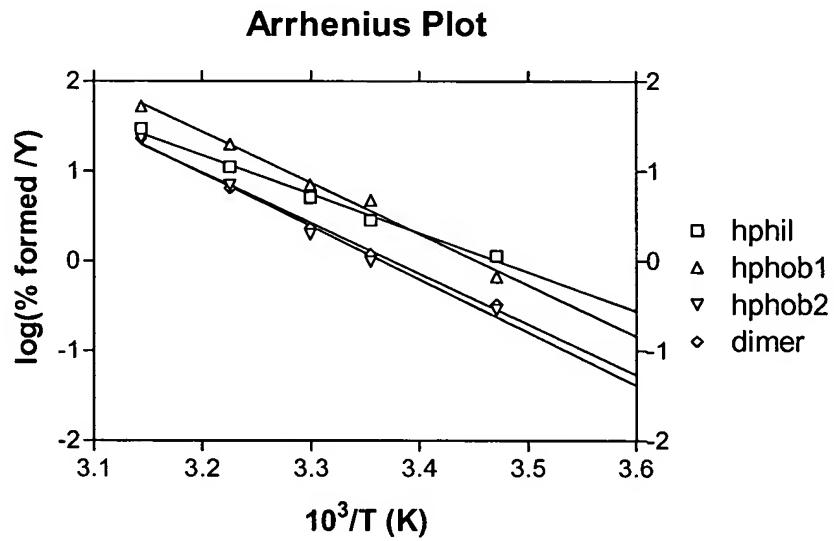
Storage in HPLC 1 ml vials at 45 °C (5 d), 37 °C (2 w), 30 °C (6 w), 25 °C (10 w), 15 °C (30 w) will give about the same increase of 0.7 % hfil, 0.6 % hfob1, 0.3 % hfob2 and 0.3 % dimer solution 1, correlating to Q₁₀ of 3 below 30 °C and 4 at higher temperature for ref..

RPC (reverse phase chromatography) on Waters SymmetryShield RP₈ column, 150×4.6 mm and 3.5 µm, eluted by A: 0.2 M sodium sulfate + 0.04 M sodium phosphate pH 7.2 + 10 % acetonitrile and isocratically (i) or a gradient (g) of B: 70 % acetonitrile [minutes/%B(i/g): 0/19, 21/24(i)(sudden change), 51/24(i), 81/39(g), 81.1/0(i), 82.3/19(i)] at flow of 0.9 mL/min and 30 °C.

SEC (size exclusion chromatography) on Waters insulin HMWP column, 300×7.8 mm, eluted by 15:20:65 of acetic acid: acetonitrile:arginine 1 g/L at flow of 1 mL/min and ambient temperature.

% formed/year	RPC			SEC
	hphil	hphob1	hphob2	dimer
45°C	29.9	52.6	23.4	23.4
37°C	11.2	20.0	7.02	6.50
30°C	5.12	7.11	1.99	2.34
25°C	2.86	4.78	0.99	1.20
15°C	1.14	0.67	0.29	0.33
5°predicted	(0.287)	(0.153)	(0.044)	(0.057)

5



Example 1016

Chemical stability of insulin formulated with the compound of example 70 , 5-(4-
10 Diethylaminobenzylidene)thiazolidine-2,4-dione

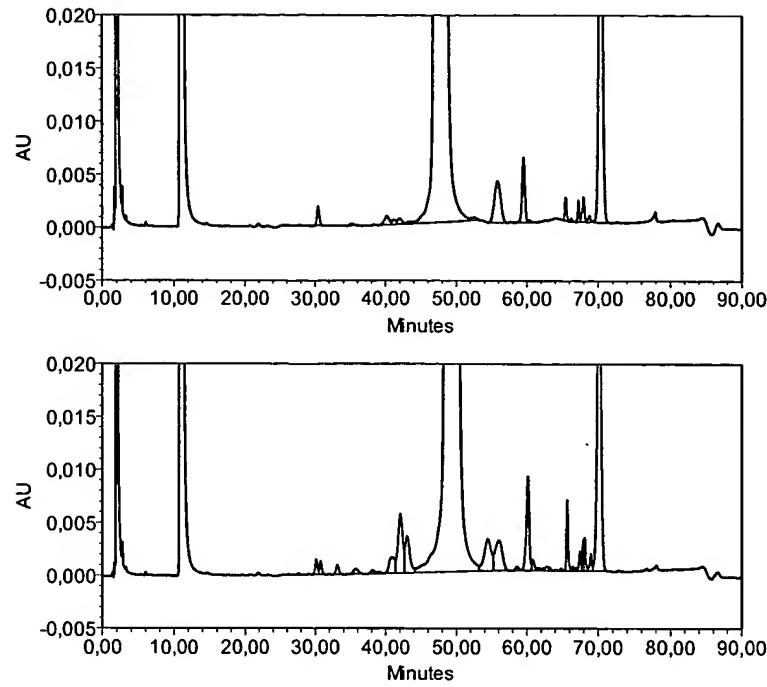


Fig 14. Reverse phase chromatography of formulated human insulin added 3 ligands (#) and 3 Zn per hexamer at start and storage of 2 w 37 °C: Preservatives before 20 min., 5 “hydrophilic derivatives” (desamido-insulins) 20 min to main top insulin, “hydrophobic derivatives 1” main top to 64 min., and “hydrophobic derivatives 2” (insulin dimers) after 64 min.

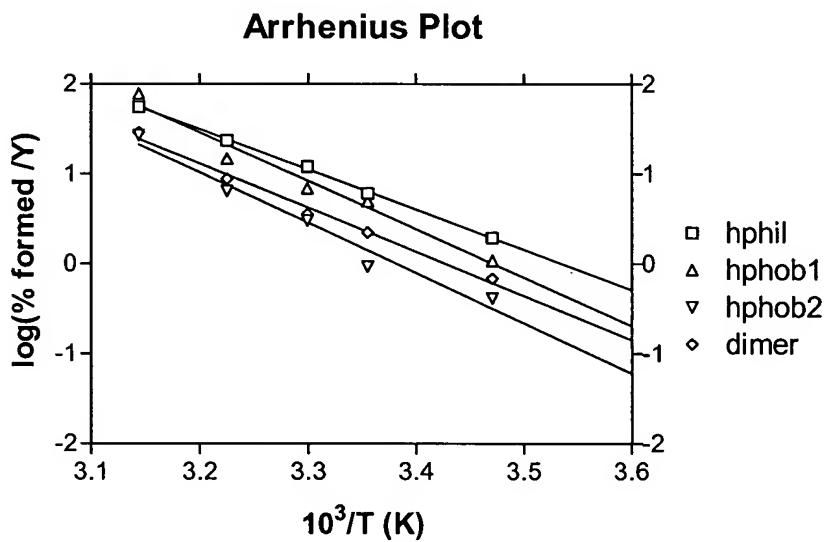
Storage in HPLC 1 ml vials at 45 °C (5 d), 37 °C (2 w), 30 °C (6 w), 25 °C (10 w), 15 °C (30 10 w) will give about the same increase of 0.7 % hfil, 0.6 % hfob1, 0.3 % hfob2 and 0.3 % dimer solution 1, correlating to Q₁₀ of 3 below 30 °C and 4 at higher temperature for ref..

RPC (reverse phase chromatography) on Waters SymmetryShield RP₈ column, 150×4.6 mm and 3.5 µm, eluted by A: 0.2 M sodium sulfate + 0.04 M sodium phosphate pH 7.2 + 10 % 15 acetonitrile and isocratically (i) or a gradient (g) of B: 70 % acetonitrile [minutes/%B(i/g): 0/19, 21/24(i)(sudden change), 51/24(i), 81/39(g), 81.1/0(i), 82.3/19(i)] at flow of 0.9 mL/min and 30 °C.

SEC (size exclusion chromatography) on Waters insulin HMWP column, 300×7.8 mm, eluted by 15:20:65 of acetic acid: acetonitrile:arginine 1 g/L at flow of 1 mL/min and ambient temperature.

% formed/year	RPC			SEC
	hphil	hphob1	hphob2	dimer
45°C	56.2	78.8	27.0	29.2
37°C	23.7	14.8	6.50	8.84
30°C	12.1	6.94	3.03	3.55
25°C	6.08	4.99	0.94	2.24
15°C	1.95	1.09	0.42	0.69
5°predicted	(0.54)	(0.22)	(0.064)	(0.15)

5



ANALYTICAL METHODS

Assays to quantify the binding affinity of ligands to the metal site of the insulin R₆ hexamers:

5 **4H3N-assay:**

The binding affinity of ligands to the metal site of insulin R₆ hexamers are measured in a UV/vis based displacement assay. The UV/vis spectrum of 3-hydroxy-4-nitro benzoic acid (4H3N) which is a known ligand for the metal site of insulin R₆ shows a shift in absorption maximum upon displacement from the metal site to the solution (Huang et al., 1997,

- 10 Biochemistry 36, 9878-9888). Titration of a ligand to a solution of insulin R₆ hexamers with 4H3N mounted in the metal site allows the binding affinity of these ligands to be determined following the reduction of absorption at 444 nm.

A stock solution with the following composition 0.2 mM human insulin, 0.067 mM Zn-acetate, 40 mM phenol, 0.101 mM 4H3N is prepared in a 10mL quantum as described below. Buffer
15 is always 50mM tris buffer adjusted to pH=8.0 with NaOH/ClO₄⁻.

1000 µL of 2.0mM human insulin in buffer

66.7 µL of 10mM Zn-acetate in buffer

20 800 µL of 500mM phenol in H₂O

201 µL of 4H3N in H₂O

7.93 ml buffer

The ligand is dissolved in DMSO to a concentration of 20 mM.

- 25 The ligand solution is titrated to a cuvette containing 2 mL stock solution and after each addition the UV/vis spectrum is measured. The titration points are listed in Table 3 below.

Table 3

ligand addition (μl)	ligand conc. (mM)	dilution factor
1	0.010	1.0005
1	0.020	1.0010
1	0.030	1.0015
2	0.050	1.0025
5	0.100	1.0050
10	0.198	1.0100
20	0.392	1.0200
20	0.583	1.0300
20	0.769	1.0400
20	0.952	1.0500

The UV/vis spectra resulting from a titration of the compound 3-hydroxy-2-naphthoic acid is shown in Figure 5. Inserted in the upper right corner is the absorbance at 444nm vs. the concentration of ligand.

The following equation is fitted to these datapoints to determine the two parameters $K_D(\text{obs})$, the observed dissociation constant, and abs_{max} the absorbance at maximal ligand concentration.

$$10 \quad \text{abs} ([\text{ligand}]_{\text{free}}) = (\text{abs}_{\text{max}} * [\text{ligand}]_{\text{free}}) / (K_D(\text{obs}) + [\text{ligand}]_{\text{free}})$$

The observed dissociation constant is recalculated to obtain the apparent dissociation constant

$$15 \quad K_D(\text{app}) = K_D(\text{obs}) / (1 + [4\text{H}_3\text{N}] / K_{4\text{H}_3\text{N}})$$

The value of $K_{4\text{H}_3\text{N}} = 50 \mu\text{M}$ is taken from Huang et al., 1997, Biochemistry 36, 9878-9888.

TZD-assay:

20 The binding affinity of ligands to the metal site of insulin R₆ hexamers are measured in a fluorescence based displacement assay. The fluorescence of 5-(4-dimethylaminobenzylidene)thiazolidine-2,4-dione (TZD) which is a ligand for the metal site of insulin R₆ is quenched upon displacement from the metal site to the solution. Titration of a ligand to a stock solution of insulin R₆ hexamers with this compound mounted in the metal

site allows the binding affinity of these ligands to be determined measuring the fluorescence at 455nm upon excitation at 410nm.

Preparation

- 5 Stock solution: 0.02 mM human insulin, 0.007 mM Zn-acetate, 40 mM phenol, 0.01 mM TZD in 50mM tris buffer adjusted to pH=8.0 with NaOH/ClO₄⁻.

The ligand is dissolved in DMSO to a concentration of 5 mM and added in aliquots to the stock solution to final concentrations of 0-250 μM.

10 Measurements

Fluorescence measurements were carried out on a Perkin Elmer Spectrofluorometer LS50B. The main absorption band was excited at 410 nm and emission was detected at 455 nm. The resolution was 10 nm and 2.5 nm for excitation and emission, respectively.

15 Data analysis

This equation is fitted to the datapoints

$$\Delta F(455\text{nm}) = \Delta F_{\max} * [\text{ligand}]_{\text{free}} / (K_D(\text{app}) * (1 + [\text{TZD}] / K_{\text{TZD}}) + [\text{ligand}]_{\text{free}})$$

K_D(app) is the apparent dissociation constant and F_{max} is the fluorescence at maximal ligand concentration. The value of K_{TZD} is measured separately to 230 nM

20

Two different fitting-procedures can be used. One in which both parameters, K_D(app) and F_{max}, are adjusted to best fit the data and a second in which the value of F_{max} is fixed (F_{max}=1) and only K_D(app) is adjusted. The given data are from the second fitting procedure. The Solver module of Microsoft Excel can be used to generate the fits from the data points.

25